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THE PROBLEM OF ARSENIC IN AMERICAN CIGARETTE TOBACCO*

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OFFICIAL declassification of tobacco as *a drug,* by its removal from the *United States Pharmacopoeia,* definitively exempted all tobacco products from control under the Pure Food and Drug Law of 1906, and so established a legal obstacle to protection of the consumer from poisonous impurities in cigarette smoke.

Thus were planted, fifty years ago, the seeds of a public-health problem that took root and developed so gradually that it was unnoticed until the report of Remington[1] in 1927. Since then, its progress has been noted at intervals,[2-4] but it has received little attention and no effective effort toward solution has been made.

The salient facts in the present phase of this problem are as follows: the arsenic content of American-tobacco cigarettes increased in twenty years from an average of 12.6 microgm. per cigarette in 1932 to 42 microgm. in 1950-51 — or more than 300 per cent; and during this time cigarette production and consumption in the United States rose by 300 per cent. The product of these two factors indicates that nine times more arsenic was distributed in cigarettes, and likewise in cigarette smoke to be inhaled by consumers, at the end of this period than at its beginning. This rise in the arsenic content of cigarette smoke coincided with an increase in the death rate from cancer of the lung of 200 per cent in women and 600 per cent in men.[5] The sequence of events, which presents a challenge to physicians interested in the public health, demands scrutiny that does not neglect study of one of the earliest features. Belated attempts at correction (since 1946) by substitution of organic pesticides for arsenicals, however commendable, cannot purify soils of tobacco plantations that have, for many years, been impregnated by residues of a heavy and relatively insoluble poison, arsenate of lead, which will continue to release, in soluble form, arsenic, which happens to be the only component of tobacco smoke that, as yet, is definitely known to be carcinogenic for man.

*Condensed from an unpublished treatise entitled "The Problem of Arsenic in Cigarette Tobacco: A corrigible phase of increasing arsenic in atmospheric environments."

Table 1 gives unpublished data on the arsenic content of American cigarettes as obtained by me and my collaborators[2,6] in 1932-34. In Table 2 these findings are combined with contemporaneous data of Gross and Nelson[3] and placed in contrast to similar findings reported twenty years later by English analysts.[7,8] Figure 1 shows graphically the increase of cigarette production and consumption in the United States to its peak, in 1952, in correlation with the rate of change in arsenic content of three types of cigarettes: American-grown, blended and Turkish-tobacco cigarettes. Interpolated in the middle period of the graph are all data[4] obtainable for the years 1942-45, when 30 per cent of the entire American production of cigarettes for 1944 was purchased by the Government for distribution to the armed forces.[9,10]

The gradually increasing values for arsenic in domestic cigarettes (Fig. 1) indicate the action of variables whose influence keeps pace with the steadily increasing rate of cigarette production. The facts point to a persistently increasing source of arsenic contamination. A likely explanation is that this results from progressive uptake by American tobacco crops of the residues of arsenate of lead that have been washed into the ground year after year to cause cumulative and well nigh permanent poisoning of the soil. The gradual release of soluble forms of arsenic and lead permits these elements to be absorbed by root systems. Such soil poisoning might well involve large areas of the land planted to tobacco — reported to average 1,677,200 acres during the decade 1942-1951.[10] This explanation of arsenic and lead impurity in tobacco is generally accepted by agricultural chemists[3] and others who have studied it, and is supported by the contrast shown in the low arsenic content of Turkish and Macedonian cigarette tobaccos. Also, it is well known that the eastern Mediterranean countries cultivate tobacco without arsenical insecticides or flue-curing processes, and have always employed primitive methods that use only barnyard fertilizer, air curing of the harvested crops and no chemical conditioning of the commercial product.

The Relation of Arsenic-Containing Smokes to Carcinogenesis, to Arsenic Metabolism, and to Increasing Arsenic in Atmospheric Environments

The problem is here formulated from basic data, without considerations of arsenoprotein sensitization or dosage factors. The recently published and revealing summary by Professor Otto Warburg[11] of his lifetime studies and conclusions on the subversive metabolism by which normal cells are changed into cancer cells distinguishes arsenic (in the form of arsenious acid) as the accepted and best known type of a chemical agent that produces cancer in man *while acting very slowly in minute dosage to poison, irreversibly, the respiration of normal cells.* This action is pictured as plunging all cells that survive its initial impact into a long-lasting dormancy or latent period of years ("sleeping cancer cells")[11] in which their respiratory function becomes ineffectual and disorganized (uncoupled from phosphorylation). Secondly, a genetic stage of adaptation for survival ensues, when the respiratory process is superseded for energizing purposes by anaerobic glycolysis, which, when predominant, is the malignant mechanism of wild and undifferentiated cell growth that denotes cancer.

Reviews of cancer caused by arsenic[12,13] stress the skin as the chief site of arsenical cancer and as the main pathway of arsenic excretion. However, other less well known channels of arsenic excretion are important sites of malignant growth. Guthmann et al.[14-17] in studies on arsenic metabolism in women, found cyclical fluctuations of arsenic concentration in the blood that depended upon activity of the reproductive system, being more than doubled during rapid growth of the embryo in the middle of pregnancy.[14] Increases in circulating arsenic were regarded as natural to all types of rapid cellular proliferation in the organism, being demonstrable in hyperplasia of uterine mucosa, in myomatosis and in 229 cases of carcinoma in women in which extensions of tumor growth were signalized by increasing arsenic transport by the blood and in which clinical improvement, which was due to radiotherapy, was marked by a drop in the blood arsenic level. As a physiologic corollary, the concentration of arsenic was greatest in organs having most active cellular metabolism, such as the lungs, thymus, gonads, thyroid gland and crystalline lens.[15] Most significant was the finding that excessive arsenic (that is, beyond normal limits in the blood) is periodically discharged from the blood stream of nonpregnant young women via the uterine mucosa and cervix uteri, and in the remark-

Table 1. *Arsenic Content of Cigarettes Examined in 1932-34.**

American-Tobacco Cigarettes ("High-Arsenic" Type)				Virginia-Turkish Blends ("Medium-Arsenic" Type)				Turkish or Macedonian Tobacco ("Low-Arsenic" Type)			
Laboratory No.	Brand No.	Date	Arsenic Content	Laboratory No.	Brand No.	Date	Arsenic Content	Laboratory No.	Brand Type	Date	Arsenic Content
			parts/ million				*parts/ million*				*parts/ million*
144, a	1	1/16/32	14.5	142, a	1-1	1/16/32	4.0	157*	2-1, specially rolled for K. Club	1/26/32	2.50
144, b	1	1/16/32	12.0	142, b	1-1	1/16/32	6.6				
590	1	4/1/33	8.0	145, a	1-2	1/16/32	5.2	158	2-2, specially rolled for F.K., M.D.	1/26/32	2.50
620, b*	1	4/12/33	9.5	145, b	1-2	1/16/32	6.6	491	2-3, specially rolled for H.S.S., M.D.	2/16/33	1.46
621, b*	1	4/12/33	9.0	596*	1-2	4/1/33	3.2				
861	1	7/6/34	24.0	155	1-3	1/26/32	4.0			Average	2.15
141, a	2	1/16/32	13.0	180	1-4	3/3/32	8.0				
141, b	2	1/16/32	12.0		"Denicotinized":						
593*	2	4/1/33	10.0	156	1-5	1/26/32	6.0				
592*	3	4/1/33	5.7	400	1-6	11/26/32	7.6				
860	3	7/6/34	16.0	435	1-6	12/2/32	(Trace)				
143	4	1/16/32	23.0		Average		5.12				
591*	4	4/1/33	17.0								
603*	5	4/1/33	20.0								
582*	6	3/26/33	10.0								
Average, 1932-34			14.31								
Summary of earliest record (from 1/16/32 to 4/12/33):											
6 brands, 13 samples											
Average			12.59								

*Items previously published[2] in exemplification of advantages of oxygen-bomb combustion analysis in tobacco testing.

ably high concentration of 320 microgm. per 100 ml., which was the average found in fresh menstrual blood.[17] These authors examined 13 patients with uterine cancer, whose mean blood arsenic concentration was 248 microgm. per 100 ml., and found in their total blood arsenic, and which averaged 40.57 per cent thereof. Concomitantly, an unidentified arsenical metabolite was isolated from the respiratory gases of the same subjects. This volatile metabolite, which is assumed to be trimethylarsine, appears to be ex-

TABLE 2. *Comparative Arsenic Content of Cigarettes Examined in 1932-34 and in 1950-51.*

1932-34				1950-51†				
PLACE OF ORIGIN	NO. OF BRANDS	NO. OF TESTS	AVERAGE ARSENIC CONTENT	PLACE OF ORIGIN	NO. OF BRANDS	NO. OF TESTS	RANGE OF ARSENIC TRIOXIDE CONTENT	MEAN OF ARSENIC TRIOXIDE CONTENT	AVERAGE ARSENIC CONTENT
			parts/ million				*parts/ million*	*parts/ million*	*parts/ million*
High-arsenic type:									
U.S. (lab. of Satterlee & Blodgett — earliest record, 1/16/32 - 4/12/33)	6	13	12.59	U.S.	3				
				England	2				
				1950 total	5	39	24.0-106.0	56.6	42.2
U.S. (lab. of Gross & Nelson, Washington, D.C.[2])	5	20	17.53	U.S. 4	1	2	46.4-46.7	46.55	33.3
				U.S. 7	1	1			
U.S. (lab. of Satterlee & Blodgett — all records, 1/16/32 - 7/6/34*)	6	15	14.31	Canada 3-1	1	4	36.8-58.2	49.3	37.4
				Canada 3-2	1	6	41.1-79.5	55.7	42.2
				Canada 3-3	1	3	42.5-57.6	47.9	36.3
				Norway 4-1	1	3	65.8-74.6	70.7	53.6
				Norway 4-2	1	4	49.7-55.6	53.0	40.3
Totals	11	35	16.15	1951 totals	7	23	36.8-79.5	53.44	40.5
Range			5.7 - 23.0	1950-51 grand totals	12	62	24.0-106.0‡	55.5	42.0
Medium-arsenic type:									
U.S. (lab. of Satterlee & Blodgett*)				Canada 3-4	1	5	8.7-18.7	12.9	9.8
				Austria 5-1	1	1	12.0	12.0	9.1
				Italy 6-1	1	6	8.3-13.7	10.26	7.76
Virginia-Turkish blends:	4	7		Switzerland 7-1	1	4	3.1-6.4	4.2	3.2
"Denicotinized":	3	3							
Totals	7	10	5.12	1951 totals	4	16		9.84	7.5
Low-arsenic type:									
U.S. (lab. of Satterlee & Blodgett*)				Austria 6-1	1	3	trace-2.1	1.16	0.87
				Poland 8-1	1	5	1.2-2.7	2.0	1.51
				Bulgaria 9-1	1	4	0.0-1.2	0.55	0.42
				Bulgaria 10-1	1	4	0.0-0.6	0.35	0.27
Turkish or Macedonian tobacco cigarettes, as custom rolled from imported leaf by New York City tobacconists:	3	3	2.15	1951 totals	4	16	0.0-2.7	1.06	0.80
				Turkish-tobacco cigarettes as sold in England (reported in 1950)	8				
				France	1	37	0.0-3.4	1.08	0.82
				Rhodesia	1				
				1950-51 totals	14	53	0.0-3.4	1.07	0.81

*From data in Table 1.

†1950-51 analyses made at St. Bartholomew's Hospital, London, reported by Daff, Doll and Kennaway[7,8]; averages converted from arsenic trioxide, parts per million, to arsenic, parts per million.

‡Range in arsenic content, 18.2-80.0 parts per million.

biopsied tumor tissues an average of 6332 microgm. per 100 ml., or twenty-five and a half times more arsenic than that found in the circulating blood of the same patients and a hundred times more than that in normal tissues.[16] These findings strongly implicate this main pathway of arsenic excretion in women with their most frequent site of lethal cancer.

Satterlee and Blodgett,[18] in examining the blood of 51 city dwellers, isolated by distillation (at 56° - 60°C.) from the venous blood, a "volatile" arsenic fraction, which ranged from 0 to 100 per cent of the creted by lungs and kidneys whenever present in the venous blood, but not otherwise. From a clinical standpoint, the arsenic in expired air and, more definitely, the volatile arsenic fraction of venous blood were considered a physiologic index of the detoxifying (methylating?) efficiency of the liver, since this fraction showed a marked reduction, and the total blood arsenic a marked increase, in unfavorable states of arsenic retention, whereas vigorous states of health gave an opposite picture. When the pulmonary excretion of arsenic, especially among city dwellers, is

considered, it seems possible that excessive inhalation of arsenical cigarette smoke, aggravated by arsenical pollution of urban atmospheres, serves to obstruct or render stagnant the bronchial current of arsenic excretion and so favors induction of bronchogenic cancer in cigarette smokers; presumably, this might occur more frequently in men, who lack the safety valve of a menstrual outlet.

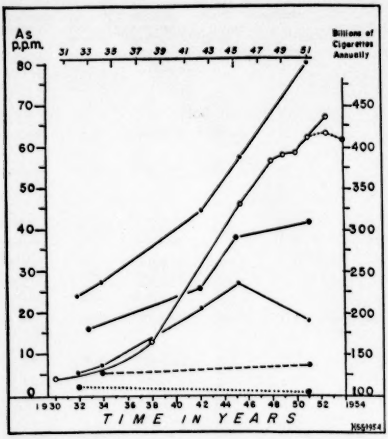

FIGURE 1. *Average and Range of Arsenic in American-Tobacco Cigarettes from 1932-1951, Compared with All-Turkish (Dotted Line) and Turkish Blends (Broken Line), in Relation to Billions of Cigarettes Produced Yearly in the United States.*

Large dots are averages, and small dots are at range limits. Solid lines refer to American cigarettes; open circles show American production and consumption to peak of 1952, and decline (broken line) in consumption from 1952 to 1954.

Analytical data (dots) for 1942-45 are from Thomas and Collier[8]; all others are as shown in Table 2. Statistics on cigarette production (circles) are from Britannica Books of the Year.[9,10]

Smoke-borne arsenic is widely prevalent whether inhaled in cigarette smoke or in more attenuated dosage as an inevitable component of ever-increasing smoke and fumes from carbonaceous-fuel combustions that pollute urban atmospheres. Preparation to examine carcinogenic potentiality calls not only for studies of arsenic metabolism in those who inhale arsenic from these sources, but also for analytical surveys covering variable sources of airborne arsenic that exist inside the home. For example, an analytical survey of sedimentary house dusts obtained by vacuum cleaner from New York City domiciles was a useful method for estimating individual exposures to arsenic, which in several cases revealed hidden or unsuspected sources of high contamination. The arsenic content of freshly collected material from 38 domiciles (83 samples) ranged from 12 to 140 and averaged 37.8 parts per million.* Assays of particles suspended in the open air (of the same city neighborhood) were made on collections taken at 30 to 90 feet above the street level. Some of these were subjected to graded filtration of the air-suspended particles in three orders of size: >30.0 - 0.75 micron; 0.7 - 0.5 micron; and 0.5 - <0.25 micron. The average weight-for-weight arsenic concentrations of these gradings were 293, 660 and 2684 parts per million, respectively.†

For a wider knowledge of arsenic content of air-suspended particles in the outdoor environment, similar filtrations were conducted from a farmhouse window 12 feet above ground level at an altitude of 1000 feet in a strictly rural district of New Hampshire during dry weather of late summer, timed at the peak of ragweed pollination and flying-insect activity. These observations, as compared with New York City findings in midwinter, yielded some surprising results. Whereas the size and arsenic content (368 and 707 parts per million) of particles collected in twenty-four hours were similar, the gross weight of material collected in twenty-four hours was only a twelfth and the entire weight only an eleventh of the values obtained for the city filtrations — as was expected. The proportion, in weight of arsenic to weight of material, was 13 per cent higher in the country than in the city, although, apparently, quite different in its nature.‡

Microscopical examination of the blackened filters containing city collections was too preponderantly obscured by soot and tarry particles for recognition of other structures that may have been present. In the country filtrations there was little discoloration of the filters, and the methyl-green-glycerin-jelly and vaselined slides exposed alongside them for morphologic examination showed mainly pollen grains (of *Ambrosia elatior*), with a scattering of spores, mycelial fragments, conidia, epithelial scales of insects, parts of feathers and animal hairs, and other unidentified organic detritus. These findings led to extensive investigations of airborne allergens,§ all of which were found to be arsenical, in the order of 7 to 112 parts per million for the fresh pollens, and 10 to 60 parts per million for the animal danders.

NEED FOR ASSAYS ON ARSENIC CONTENT OF CITY AIR AND ARSENIC METABOLISM IN CIGARETTE SMOKERS AND CITY DWELLERS

Accurate estimates of respiratory intake of arsenic by city dwellers are obviously important and should be

*As pointed out in Table 3, Section A, of the unpublished treatise on which this paper is based.

†These results are considered in detail in Table 4, Section A, of the unpublished treatise on which this paper is based.

‡This apparent incongruity disappears with the reflection that all airborne arsenic that is contained in the smoke and fumes from fuel combustions of coal, petroleum oils and natural gas, as well as in the carbon-black components of synthetic-rubber tires, road tars and so forth, is without exception of *paleozoic origin*. It is in fact, *fossilized arsenic*, which, before man's appearance on this planet, functioned as an essential chemical component of plant and animal life that flourished and perished in fabulous profusion throughout the Carboniferous Era.

§Detailed in Table 3, Section C, of the unpublished treatise on which this paper is based.

undertaken only on a volumetric basis. On this basis it seems that there have been fallacious estimates, dubious technics and misleading conclusions that have been widely accepted. For accuracy in this undertaking it is essential that all volatile losses be prevented by immediate extraction of small samples of town air at the time of collection and prompt assay, to capture volatile arsenic in watery vapors and invisible fumes, as well as in particulate matter.* Environmental and occupational samples of air taken from outdoors are not representative of true breathing conditions, since they do not pertain to important intramural sources of arsenic contamination.† Such samples should, therefore, be taken within the home, office, factory or workshop. This may be done quite easily with a portable suction device in connection with an absorption train, attached to a volumetric collecting system. Such a method has proved its efficiency in the routine testing of 2-liter to 10-liter samples of laboratory air for "background arsenic," which, in twelve years of practice in New York City, ranged from 0.1 to 0.4 microgm. per 10 liters, or from 10 to 40 microgm. per cubic meter.‡ With the addition of a basal-metabolism face mask, the same apparatus was used for the expired-air test, in which the arsenic concentrations ranged from nothing to 1 microgm. per 2 liters.[18] In both procedures the collecting and measuring system was a pair of 2-liter leveling bottles (Pyrex) in stopcock connection with a vacuum-operated absorption train.[18] The train was later simplified to consist of 2 (or 3) gas-dispersing (fritted-glass, Pyrex) units, immersed in side-arm test tubes, each containing 6 to 10 ml. of appropriate solvents. When the run is completed, the entrained arsenic (in acid solution) is promptly removed for immediate or later testing by vacuum-Gutzeit spot filtration.[18]

For a better understanding of normal and faulty arsenic metabolism (as in arsenicism), there is an obvious need positively to identify the volatile-arsenic component of venous blood which, quite evidently, is either the same as, or else the immediate precursor of, "expired-air arsenic." This arsenic metabolite may be assumed to be the fully methylated and relatively nontoxic trimethylarsine, which is a water-soluble liquid having a vapor pressure of 266 mm. at 20° and 762 mm. at 49.5°C.[19] The studies of Challenger[20] show that the metabolism of trimethylarsine by mammalian organisms may be assumed to parallel that of its chemical analogue, dimethyl selenide, which is a similar (relatively nontoxic) form of selenium that is fully methylated (by hepatic(?) enzymes) in the rat. Synthetic dimethyl selenide is harmlessly and rapidly excreted by the lungs of the rat after parenteral administration, and it is excreted by the lungs *after the subcutaneous injection of inorganic selenium.* This phenomenon was brilliantly demonstrated by McConnell and Portman,[21] with positive identification of the volatile metabolite that they isolated from the respiratory gases. It was accomplished by means of a double experiment. As the first step, white rats in a bell jar were injected subcutaneously with dimethyl selenide in considerable dosage (0.845 gm. per kilogram of body weight), and their expired air was aspirated through an extraction train containing bichloride of mercury solution, which precipitated the excreted selenium as the dimethyl-selenide-bichloride of mercury derivative, of which a plentiful and rapid recovery was obtained with identification of the substance by melting point of its crystals and by elementary analysis. As the second part of the experiment, inorganic labeled selenium (radioselenate) was injected into four groups of rats that were subjected to the same process of extraction of their respiratory gases; here, the metabolic conversion and excretion of the volatile product was slow and without visible sign for six hours, at which time imponderable quantities of dimethyl selenide were isolated by carrier technic and identified by specific activity (in counts per minute) as a component of the mercuric halide complex, which was purposely precipitated in the train to act as a carrier. Identification, by specific radioactivity of crystals, was performed in three ways. This double experimental procedure provides a unique pattern by which the so-far-unattained identification of "expired-air arsenic" (and its precursor in the blood) may be safely achieved in the human subject after pilot experiments in the rat; it is a purpose of this communication to point out the importance of accomplishing this task as an essential step toward ascertaining if complete methylation of the arsenic atom (displacing its oxygen linkage in the trivalent state) is a defense reaction that abolishes its irreversible inhibiting effect on cellular respiration and favors its harmless elimination from the organism. Availability, from various institutional laboratories, of the cyclotron-produced isotope complex $As^{73}-As^{74}$, with half lives of 90 and 19 days respectively, as formerly produced by the Oak Ridge National Laboratory in the form of arsenic trichloride in hydrochloric acid solution, supplies an agent that is suitable for the synthesis of a radioactive trimethylarsine by condensation on zinc methyl.[19]

*A summary of such attempts at extraction is presented in the notes to Table 3 of the unpublished treatise on which this paper is based.

†Notes on the excessive background arsenic in laboratory practice are presented in the appendix to the unpublished treatise on which this paper is based.

‡At this rating, which averaged 25 microgm. of arsenic per cubic meter, or 33 microgm. of arsenic trioxide per cubic meter, and estimating the daily volume of air breathed by "the standard man" as 20 cubic meters, the "background arsenic" inhaled by a worker in a New York City laboratory under favorable conditions (as in 1932-45) would be 0.66 mg. of arsenic trioxide in twenty-four hours, which is a yearly intake of 241 mg. of arsenic trioxide, or the equivalent of 48 maximum official doses of Fowler's solution. It should be noted, however, that in another large city in November, 1948, the laboratory "background arsenic" in an institutional building ranged as high as 222 microgm. of arsenic trioxide per cubic meter, or more than four times the tolerance limit, as pointed out in the appendix to the unpublished treatise on which this paper is based. If the laboratory technician (or worker in a city workshop) happens to smoke a package of cigarettes a day, inhaling 10 per cent of 50 microgm. of arsenic trioxide with each cigarette,[1] he would add 36.5 mg. per year to his atmospheric intake of arsenic, but this cigarette arsenic would reach his lungs intermittently as a freshly distilled sublimate interspersed in fluorescent smoke particles, and in a concentration a hundred times greater — that is, from 3.3 to 10.5 mg. of arsenic trioxide per cubic meter,[4] as against 33 microgm. of arsenic trioxide per cubic meter for a normal background concentration.

The recent work of Sweet and Brownell[22,23] on diagnosis and localization of brain tumors in early stages of growth by employing a similar isotope (As^{74}-emitting positrons), has shown that radioarsenic injected intravenously as arsenite or arsenate has a tenfold selective affinity for tumor tissue as compared to normal brain tissue. The scanning system devised by them, with opposed and collimated twin scintillation counters connected in a coincidence circuit, seems applicable to exploration of the lungs when potentially cancerous lesions might be expected to exist. Whether radioactive trimethylarsine would be a more effectual tracer in such conditions is an interesting question. Some diagnostic procedure of this kind seems highly desirable for application to inveterate cigarette smokers with respiratory symptoms.

Summary

Analytical data are presented to show that the arsenic content of various popular brands of American-tobacco cigarettes averaged 12.6 microgm. per cigarette as sold in 1932-33, and that in comparison with the data published in 1950-51, the arsenic content increased to 42 microgm. per cigarette, or more than 300 per cent in twenty years; this increase is attributed to the use of arsenical pesticides on American tobacco plantations.

Statistics are cited to show that cigarette smoking, as indicated by production and sales, increased more than 300 per cent in the same twenty years, and that the death rate from lung cancer in the United States rose 200 per cent in women and 600 per cent in men during a twenty-year period ending in 1954.

The data cited are regarded as relevant to one phase of a public-health problem that is concerned with the wider question of arsenical cancer, and also with the closely related problem of increasing airborne arsenic in urban atmospheres that are polluted by arsenic derived from petroleum-fuel combustions, both indoors and outdoors, and by airborne arsenical detritus from the abrasion of synthetic-rubber tires and tarred or oiled roads. Reliable data in this field are lacking and are desirable in many localities.

Analytical data on graded filtrations of air-suspended particles show that the arsenic content of such particles is unstable and that it varies inversely with particle size. Strict precautions are needed to avoid volatile-loss errors in assays of such material. An improved method is recommended for indoor collection and immediate acid extraction of small volumes of air when microdeterminations of "background arsenic" in any situation are made.

The significance of arsenic excretion through the genitourinary tract and through the respiratory tract is examined in relation to neoplastic disease of these tracts, and also in relation to sex differences in arsenic excretion.

The importance of seeking better knowledge of arsenic metabolism in relation to carcinogenesis, by more searching and precise methods of chemical and physical investigation, is stressed. Special technics for employing radioarsenic are regarded as promising implementation for clarifying the problem of airborne arsenic and smoke-borne arsenic in relation to lung cancer occurring in cigarette smokers and in others who live in air-polluted industrial cities.

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ON CIGARETTE SMOKING, BRONCHIAL CARCINOMA AND CILIARY ACTION*

II. Experimental Study on the Filtering Action of Cow's Lungs, the Deposition of Tar in the Bronchial Tree and Removal by Ciliary Action

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THE *New York Times* published a story in February, 1955, stating that bronchogenic carcinoma never develops in the Yemen Jews.[1] They smoke a great deal of strong tobacco but pass the smoke through water in a special type of pipe.

One wonders what becomes of the smoke after it leaves the proximal end of American cigarettes. It passes directly, of course, into the mouth. Hansel[2] has described the effects of tobacco smoking on the upper respiratory tract. Proetz[3] has studied the irritating effects on the pharyngeal mucosa and has demonstrated tar deposit in the noses of experimental animals. So-called smoker's throat is familiar to all laryngologists, as is the so-called "tobacco cough". Roth[4] and Friedell[5] have shown effects on the circulation that they think indicate absorption of nicotine. It is obvious that something is deposited to make these objective and subjective changes.

When a smoker aspirates smoke from his cigarette, the end from which it emits is invariably out of sight in his mouth. One becomes curious to know what the smoke looks like as it comes from the end of the cigarette, under pressure. How does a short puff of half a second look as compared with a long one of four seconds? What happens when the pressure is increased from 40 to 400 mm. of water — the former being the pressure of a low-pressure puff, and the latter that of a high one? How much of the smoke deposits and how much returns with expiration? If part of it deposits or condenses, where does deposition occur? How rapidly does deposition occur?

The technics or habits of smoking were discussed in an earlier study[6] describing the number and duration of puffs and the pressures used. What the smoker does with the smoke after it enters his mouth is another story. There are many individual variations in the manner of handling and toying with the smoke. Some smokers open the mouth widely, exposing the dense smoke to view, and some extrude it partially from the mouth and then aspirate once more. From these maneuvers, one may obtain an impression of what the smoke looks like before it is inhaled. Most smokers eventually inhale it into the lungs, no matter how they may toy with it first. When it returns, it is much less dense and looks bluish. This is undoubtedly due in part to dilution, but experiments reported below show that it is also due in part to deposition of the smoke ingredients. The longer it is retained, the less dense and more blue it appears when it returns.

Attempts were made to time with a stopwatch the period during which the smoke is retained and to relate this to the reduction of visible smoke. Readings of around four to four and a half seconds were obtained, but it is difficult to determine this because there is no definite end point of smoke flow, during either inspiration or expiration. The time depends a great deal upon the rate of respiration. Most smokers do not actually "hold the breath," but some breathe so slowly that they seem to do so.

SMOKING APPARATUS

A simple apparatus was designed for smoking cigarettes in such a way as to make the smoke visible and to deliver it in a continuous stream or in puffs of any desired duration and at any desired pressure (Fig. 1). It consists of a cylindrical glass burning chamber 3 cm. in diameter and 15 cm. in length. A cigarette holder in a rubber stopper closes one end and holds the cigarette within the chamber. Compressed air is delivered into the other end of the chamber and escapes by passing through the cigarette. The smoking chamber is connected with a glass "Y", one arm of which is connected with a source of compressed air and the other arm with a second and a third "Y". The second "Y" vents into the room through a rubber tube through which the air is allowed to escape between puffs (when compressed, the air is forced through the cigarette and into the manometer), and the third "Y" connects to a manometer and a bottle containing a column of water of the length to be used as the upper limit of the desired pressure (a safety-valve arrangement). In addition, a crossventilation is provided at the proximal end of the burning chamber to keep the cigarette burning between puffs. A rubber tube from this crossventilator is fastened across the air escape tube so that the two can be compressed together. When the two tubes are compressed with a finger, the air is forced through the cigarette and into the manometer and water bottle. If the pressure exceeds that of a column of water equal to the depth of the water in the bottle, the air escapes through the bottle and limits the pressure of the air passing through the cigarette.

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It was found in a previous study[6] that the duration of smokers' puffs varied between half a second and four seconds. Most of the puffs ranged between one and three seconds. The pressures used in smoking (pressure difference between the two ends of the cigarettes) also varied widely. As measured in volunteers, on a water manometer and a mercury manometer, these pressures ranged between 40 and 450 mm. of water.

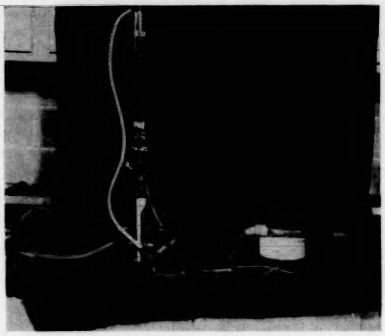

FIGURE 1. *Smoking Apparatus Used in Imitation of Smokers' Puffs and in Passing of Smoke into the Cows' Lungs. By pressure on the cross tubes in the foreground the air was made to pass through the smoking chamber and cigarette.*

Cigarettes were smoked in the apparatus described at pressures of 50, 100, 150 and 200 mm. of water, steadily and in puffs. The puffs were timed at half a second, one second, two seconds and four seconds at each of the various pressures used and all were photographed (Fig. 2-4).

It soon became apparent that the hotter the burning end became, the less dense and more blue the smoke became. In other words, either burning steadily or in long puffs at the higher pressures, the combustion was more complete, and the smoke less dense. Chemical analyses of combustion products from varying temperatures of burning, made by others,[7,8] indicate that the chemical composition of the combustion products varies significantly at different temperatures. In steady, continuous burning, the densest smoke appeared at low pressures — 20 to 50 mm. of water. Therefore, to imitate the clouds of smoke from smokers' puffs, it was necessary to remove the cigarette between puffs and let it cool for half a minute or more, as a smoker does.

The striking finding in these tests, as judged by the eye, was that the cigarettes smoked in the apparatus, at all the different pressures used and with all the different lengths of puffs (from half a second to four seconds), produced far greater quantities of smoke than smokers exhale with similar puffs.

ANIMAL MATERIAL AND TECHNIC

The tracheas and lungs of freshly killed beef animals furnished the experimental material used in these studies. The lungs and tracheas were obtained intact upon the killing floor within a few minutes of death. They were immediately placed in a warm box, which had been especially constructed to prevent drying and cooling. The ciliated respiratory epithelium will live and remain active for many hours if kept warm and moist. Ventilation does not seem to be necessary. The upward streaming of the mucous blanket, motivated by ciliary activity, can be studied for hours. It seems that the mucous blanket present at the time of death would soon be swept away and not replaced. I do not know how long the mucous glands continue to secrete after death, but, under proper conditions, the ciliary streaming, as evidenced by visible material carried along on the mucous blanket, can be observed for hours.

The tracheas and lungs of 15 freshly killed cows or calves were used in these experiments. Each was prepared in such a way that cigarette smoke from the apparatus could be passed into the upper end of the trachea. The lower third of both lungs was amputated, and then the upper end of the trachea connected to the smoke chamber. Eleven were laid horizontally on the table with the anterior surface

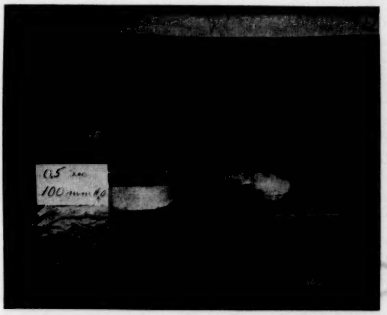

FIGURE 2. *Illustrative Puff Half a Second in Duration and at a Pressure of 100 Mm. of Water. The ruler is 30.5 cm. long. The average smoker does not exhale such a large quantity of smoke as that illustrated.*

down, and four were mounted in the vertical position suspended by the trachea. When smoke was directed into the trachea in either position, it passed readily through the air passages and escaped from the cut ends of the bronchi.

The amount of smoke passed into the specimens was measured in a number of different ways. In 4 specimens 2 to 5 cigarettes were smoked more or less completely. In 1, a single cigarette was smoked for five minutes at a pressure equivalent to 50 mm. of

water. Five were measured in millimeters of cigarette burned, and 5 in the number of puffs at a pressure of 40 mm. of water. The puffs were two, three or four seconds in duration and were made twice a minute. The simplest and best way of measuring was found to be in terms of millimeters of cigarette burned at a given pressure (40 mm. of water).

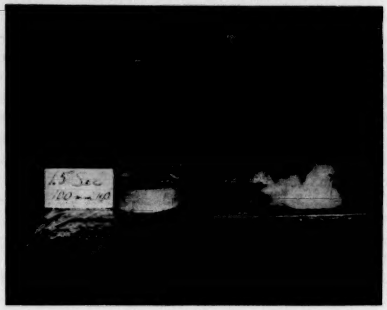

FIGURE 3. *Illustrative Puff One and a Half Seconds in Duration and at a Pressure of 100 Mm. of Water. The puffs of an average smoker would range between the amount shown here and that indicated in Figure 4.*

FILTERING ACTION OF THE LUNGS

When cigarettes were burned in the apparatus described and the smoke passed into the trachea of such a lung preparation, it passed through the larger air passages and was seen to come out at the cut surface through the larger bronchi. The smoke appeared thin and bluish in contrast to the dense smoke entering at the trachea. When the larger bronchi, from which the smoke was escaping, were clamped, smoke came from the smaller bronchi, but in smaller quantities, and it appeared still thinner and more blue. When these, in turn, were progressively clamped and the smoke and air forced to flow through tiny passages, the visible smoke eventually disappeared entirely. The resistance to flow increased, but at a pressure of 50 mm. the cigarettes burned well and delivered the smoke ino the trachea. The smoke was filtered from the flowing air by the lungs so completely that no smoke could be seen coming from the cut surface.

This experiment was repeated on a number of different lung specimens with the same results. Cigarette smoke can be so completely filtered in a few seconds while passing once through the upper two thirds of a cow's lung that no visible smoke remains.

DEPOSIT OF TAR

Proetz[9] performed experiments in which he blew smoke from his mouth into a box and observed the length of time required for deposition of tar. In five minutes there was comparatively little deposit; ten or fifteen minutes were required for a substantial deposit. Unlike the smoke in Proetz's box, the smoke that passed through the lungs in the present experiments deposited rapidly. When the bronchial trees were opened, a definite, yellow film, presumably of tar deposit, was noted in 10 of the 15, and in another there was a ring of tar-containing mucus at the upper (cut) end, where it had been carried by ciliary action. In 1 there was no record. Among the other 3, 1 had received 10 puffs of three seconds' duration, and the others 17 and 18 puffs respectively of two seconds' duration. A film of tar was undoubtedly present in these also but was too faint to show definitely. These 3 were all "smoked" in the vertical position. One of the 4 smoked in this position contained a visible film. The film was evenly spread over the entire circumference of the air passages. The other 9, of the 10 that contained yellow films, were smoked in the horizontal position with the anterior surface down on the table — dependent. The film was anterior in all 9 of these. The smoke, being heavier than air, had flowed along the dependent anterior third or half of the air passages and deposited there. The deposit was heaviest at the cephalic end, becoming somewhat less heavy as the coryna was approached, and became invisible in the bronchi.

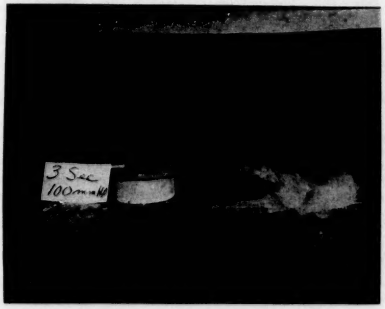

FIGURE 4. *Illustrative Puff Three Seconds in Duration.*

EFFECT ON CILIARY STREAMING

Ciliary streaming can be demonstrated readily in these excised respiratory tracts of freshly killed animals. It continues for hours under the circumstances of these experiments. Only 3 of these 15 were opened and tested before the cigarettes were smoked into the trachea. All 3 showed ciliary streaming directed toward the laryngeal end of the trachea. Of the 10 that showed a definite yellow film after smoking, 6 were devoid of ciliary action; 4 showed some degree. Apparently, when a visible deposit occurs, the ciliary action is apt to cease. In the 4 exceptions (Cows 13

and 28 and Calves 17 and 18), there was some streaming. These four are worth describing separately.

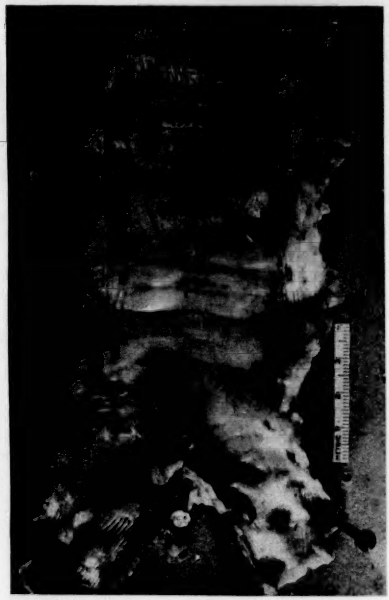

FIGURE 5. *Distribution of the Tar in the Trachea of Cow 28.*

No photograph of this specimen was obtained; for that reason the findings were sketched in on another trachea. The stippled area represents a yellow film of tar under which there seemed to be no ciliary action. The black lines represent long, thin cords of mucus densely packed with tar, which had been swept off the areas below and collected here at the edge of the area in which ciliary action had ceased. Caudad and posterior to the cords of tar-laden mucus, the epithelium was clean and shiny and, as far as could be determined, free of tar.

The yellow deposit in all was heaviest in the cephalic portions of the trachea — the portions closest to the source of smoke. It became light enough in the deeper (caudal) portions of the trachea so that ciliary streaming remained active. In 1 (Cow 13) the smoke from one cigarette burning with a pressure of 50 mm. had been delivered into the trachea for a period of five minutes. The yellow deposit covered the anterior dependent portion of the trachea down to a point 10 cm. above the coryna, below which there was no yellow discoloration. At that point, there was a crescentic accumulation of very yellow mucus (tar laden, supposedly) extending across the trachea. Apparently, the ciliary streaming had carried the mucous blanket upward, together with the contained tar, to a point 10 cm. cephalad from the coryna, where ciliary action ceased. There, the mucous blanket came to a standstill and accumulated. The difference in appearance between the clean areas caudad to the accumulation (upstream) and the discolored areas cephalad, where the yellow film lay, was most striking. The dividing line was very sharp. Calf 18, into which 20 mm. of cigarette had been smoked at a pressure of 45 mm., presented a similar picture.

The picture was even more striking in another (Cow 28). Three cigarettes had been smoked into this trachea in the form of 2 puffs per minute of a duration of four seconds each and at a pressure of 40 mm. of water. The smoke was first passed through a cooling tube. When the trachea was opened, it was found that a yellow film covered the mucosa down to a point 10 cm. above the coryna. It was heaviest at the cephalic end of the trachea and in the anterior dependent portion and obviously had not moved since it was deposited. Caudad from a point 10 cm. above the coryna, some ciliary streaming was preserved posteriorly and laterally. This was found in the highest part of the trachea as it lay on its anterior surface. These areas were swept clean of tar, which had accumulated in sharply defined ropes of mucus lying diagonally across the lateral walls (Fig. 5). The mucus-laden tar had been swept off the areas where ciliary action was present and deposited along the boundary line delimiting the areas devoid of ciliary action.

In the remaining animal (Calf 17) there was a faint but definite yellow film covering the mucous surfaces. Ciliary action seemed to be everywhere present because the whole film was moving more or less normally.

CHANGE IN CHARACTER OF SECRETION

A definite change in the character of the mucous blanket was noted in 4 of the tracheas containing yellow films of deposit. At least a part of the blanket had become watery and had collected in the anterior dependent portion. On this watery fluid, the cigarette tar floated as a thin scum. Generally, no ciliary action was demonstrable under this thin, watery secretion. In the single exception to this, India ink, which had been placed upstream, was carried along under the surface scum, which remained stationary.

ACTION OF SMOKE ON CILIA

As a further test of the effect of smoke on ciliary action 3 experiments were done in which scrapings of live epithelium were placed in hanging drops under the microscope, and the beating cilia observed directly. In each a jet of cigarette smoke was played over a small amount of Ringer's solution in a watch glass, after which a very scanty film of material could be seen under the microscope to be floating upon the

surface. It was not visible grossly. One hanging drop was made from this solution, and another from the same Ringer's solution without exposure to smoke. A small piece of live epithelium was placed in each hanging drop and examined under the microscope.

The experiment was repeated three times. In the first two, the cilia were immobile in the drop exposed to smoke and action was present in both controls. In the third experiment, ciliary action was present in each when the specimen was first observed, but, when it was looked at again after eleven minutes, ciliary action had ceased in the test specimen whereas it continued in the control. The control specimen was observed for an hour, and the action was still good at the end of that time. Obviously, some substance or substances, toxic to ciliated cells, had been dissolved — probably nicotine, for one. It is known that nicotine, if sufficiently concentrated, will stop ciliary action.

Discussion

A number of points about cigarette smoke and the tracheobronchial tree become clear from these studies, and the questions posed at the beginning may be answered.

When cigarettes are burned in an apparatus devised to imitate the pressures and puffs used by cigarette smokers, they deliver much more smoke than smokers return with expiration.

The quantity of smoke that the cigarette delivers is generally proportionate to the length of the puff and the amount of pressure used, if the temperature remains constant, except that it takes a fraction of a second for the cigarette to "get going." If the temperature of burning is increased, the quantity of visible smoke decreases, and (as indicated by the work of others) the chemical composition varies.

In these bovine-lung preparations, when the smoke emerged from the larger bronchi at the cut surface of the lung, it was much less dense and more blue than when passed from the cigarette into the trachea. A large proportion of it was deposited on the walls of the air passages in the form of a thin, brownish-yellow film. The deposit was greatest at the proximal end of the trachea and diminished progressively toward the coryna. It was usually not visible in the bronchi, not only because most of the tar had been deposited before the bronchi were reached but also because the area of the mucous membrane increases with each subsequent division and the tar deposit is spread more thinly over the increased area.

When the larger bronchi were clamped and the smoke and air were forced to pass through smaller bronchioles, the smoke was filtered out so completely as to become invisible. If the smoke is handled in a similar manner in the bronchial tree of smokers, it seems to follow that smoke reaching the tiny air passages is largely deposited and what returns with expiration is mainly the amount that lies in the larger air passages. Perhaps little or no smoke actually reaches the alveoli.

The time required for deposition of tar in these lung preparations was a matter of seconds only. No apparent reason suggests itself for believing that tar is not deposited in a smoker's lungs with equal rapidity.

Deposition occurs upon the mucous blanket that normally lines the tract. A portion quickly dissolves and enters the ciliated cells. This is toxic and, if sufficiently concentrated, quickly destroys ciliary action, as shown by the microscopical tests on living ciliated cells. This soluble portion could be composed of nicotine or other toxic substances or could be nicotine combined with other toxic substances. If the deposited film of tar is dense enough to be readily visible, enough toxic material has dissolved, in many cases, to destroy ciliary action.

If ciliary action is retained, then the scum of tar is carried toward the larynx upon or in the mucous blanket with the normal ciliary streaming. Presumably, this is what happens in smokers. It is scarcely imaginable that the concentration of dissolved toxic materials could be sufficient to stop ciliary action generally because cessation of ciliary activity in the tracheobronchial tree is incompatible with life. Cigarette tar must be carried out of the tract and delivered with the mucous blanket into the laryngeal pharynx to be swallowed into the stomach.

Conclusions

When cigarette smokers inhale cigarette smoke, a large proportion of the ingredients are retained. The time required for deposition is very brief, being a matter of seconds only. These ingredients are deposited upon and in the mucous blanket, where toxic substances are quickly dissolved and absorbed into the mucous membrane.

If the toxic materials are sufficiently concentrated, ciliary action ceases.

A visible scum of tar remains floating on the mucous blanket, and, if ciliary action is retained, is carried with the mucous blanket to the laryngeal end of the trachea.

These studies are being continued and further reports will follow.

Since this article was received for publication, tests have been made indicating that smoke does not deposit quite as rapidly in the lungs of smokers as in the cow's lungs, probably because the latter are partially collapsed and many of the finer passages closed or nearly so.

I am indebted to the Elliott Packing Company, Duluth, Minnesota, for furnishing the animal specimens used in this study.

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THE L. E.-CELL PHENOMENON IN CHRONIC HEPATIC DISEASE*

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CHICAGO

THE L. E.-cell phenomenon has been considered to be specific for systemic lupus erythematosus.[1-6] Several large surveys have not revealed any false-positive L. E. tests.[1-6] Nevertheless, its occurrence has been reported in other pathologic states such as multiple myeloma, pernicious anemia and moniliasis,[7-10] in hypersensitivity reactions[11,12] and in the rheumatoid syndrome after treatment with hydralazine.[13,14] It has been emphasized that in patients with *drug* hypersensitivity, cells undergoing nucleophagocytosis may simulate the L. E. cell.[15-18] In other cases of hypersensitivity reactions, and in the syndrome that follows hydralazine therapy, cells indistinguishable from classic L. E. cells have been found.[11-14] The demonstration of a positive L. E. test in diseases other than systemic lupus erythematosus is important, since it not only reflects on the specificity of the procedure but also may provide clues to a better understanding of the L. E.-cell phenomenon.

During the past year several reports of positive L. E. tests in patients with chronic hepatic disease have appeared.[19-22] The present communication deals with 2 additional patients with cirrhosis of the liver exhibiting a positive L. E.-cell phenomenon.

TABLE 1. *Liver-Function Tests in Case 1.*

DATE	TOTAL BILIRUBIN		DIRECT BILIRUBIN		BROMSULFALEIN RETENTION		THYMOL TURBIDITY		CEPHALIN FLOCCULATION		SERUM ALBUMIN	
	NORMAL VALUE	PATIENT'S VALUE	NORMAL VALUE	PATIENT'S VALUE	NORMAL VALUE	PATIENT'S VALUE	NORMAL VALUE	PATIENT'S VALUE	NORMAL VALUE	PATIENT'S VALUE	NORMAL VALUE	PATIENT'S VALUE
	mg./100 ml.	*mg./100 ml.*	*mg./100 ml.*	*mg./100 ml.*	*% per 45 min.*	*% per 45 min.*	*units*	*units*	*in 48 hr.*	*in 48 hr.*	*gm./100 ml.*	*gm./100 ml.*
6/11/54	0.7	7.9	0.4	3.0	<5	45.0	<4	17.4	0 - ++	+++	4.5 - 5.5	2.3
6/28/54		3.4		2.0		29.5		11.7		+++		2.2
8/3/54		2.5		1.1		35.0		14.6		++++		2.7
9/2/54		2.5		0.7		37.0		14.6		++++		3.0
10/18/54		2.3		0.7		33.0		11.3		++++		3.1
11/23/54		2.3		0.5		—		—		+++		3.5
3/8/55		1.5		0.3		17.0		6.2		+		4.3
6/1/55		1.1		0.5		26.0		6.7		—		3.9

CASE REPORTS

CASE 1. T. B., a 33-year-old freight-yard worker, was admitted to the Veterans Administration West Side Hospital, in June, 1954, because of gradually increasing jaundice and swelling of the abdomen and legs. These symptoms had started about 6 weeks previously. He had been drinking large amounts of beer daily since the age of 14.

Physical examination disclosed moderately severe jaundice and anxiety, with mild tremor. Ascites and edema of the lower extremities were marked. Numerous spider angiomas were present on the skin of the thorax, upper extremities and forehead. There was no hair on the chest. Marked fetor hepaticus was noted. The liver was palpable 8 cm., and the spleen 3 cm. below the respective costal margins.

There was a mild normochromic, normocytic anemia, with a hemoglobin level of 11.5 gm. per 100 ml.; the white-cell and differential counts and platelet level were normal. A trace of bilirubin was found in the urine, which was otherwise normal. The results of the liver-function tests are summarized in Table 1. The protein pattern as obtained by filter-paper electrophoresis is presented in Figure 1. Electrocardiograms were normal, and x-ray examinations of the chest and upper and lower gastrointestinal tract were negative. Three liver biopsies (Fig. 2), performed between September, 1954, and February, 1955, gave evidence of

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pseudolobules separated by broad bands of fibrous tissue. These fibrotic areas contained inflammatory foci, considerable vascularization and proliferating bile ducts. Fatty metamorphosis of hepatic cells was conspicuously absent.

Treatment with bed rest and a "low-salt" diet was followed by marked diuresis and weight loss. Crude liver extract (Armour) was administered intramuscularly each day for 10 weeks. Jaundice and nutritional status improved gradually; edema and fetor hepaticus disappeared within several weeks, but the hepatosplenomegaly decreased only slightly. Three months after admission pneumonia developed, with pneumococci demonstrable in the sputum. There was a prompt response to penicillin. Because of an unrelated research project" an L. E. test was done before the use of penicillin. To our surprise numerous L. E. cells were noted (Fig. 3). Clinical improvement of the liver disease continued steadily despite the persistent finding of L. E. cells. The patient was seen for the last time in September, 1955, when he felt well, although the hepatosplenomegaly and spider angiomas were still present. Results of liver-function tests were still slightly abnormal (Table 1). The L. E. test also was positive.

CASE 2. A. G., a 21-year-old Negress, was admitted to Michael Reese Hospital in coma in April, 1955. Four days previously admission she had become drowsy and forgetful and on the day of admission could not be awakened. In July, 1954, while in her 6th month of pregnancy, jaundice, malaise, anorexia and generalized pruritus had developed. A diagnosis of infectious hepatitis was made. She was admitted to another hospital but stayed there only 12 days, and then resumed her housework despite persistence of symptoms. In August, 1954, she was delivered prematurely, but spontaneously, of a living infant. At the time of delivery she was still jaundiced. She was readmitted to the same hospital 3 months later because of swelling of both lower legs, chills and fever and persistent jaundice. She stayed at that hospital until the end of January, 1955. A diagnosis of chronic hepatitis, pyelonephritis and anemia was made, and she was treated with blood transfusions, high-protein diet, vitamins and tetracycline. During this stay in the hospital, widening of the cardiac silhouette, attributed to a pericardial effusion, developed. The cardiac enlargement disappeared and within 2 weeks the patient was discharged, although the jaundice persisted.

On admission to Michael Reese Hospital she was comatose and jaundiced and had fetor hepaticus. There was mild nuchal rigidity. The liver and spleen were not palpable. The deep tendon reflexes were hyperactive.

The temperature was 99.8°F., the pulse 96, and the respirations 22. The blood pressure was 100/90.

The urine had a specific gravity of 1.005 and gave a + + test for albumin and a + + + + test for bilirubin; the sediment contained 3-5 red blood cells and an approximately equal number of white blood cells, hyaline casts and finely granular and coarsely granular casts per high-power field. Urine cultures were negative. Examination of the blood revealed a hemoglobin of 7.3 gm. per 100 ml. and a white-cell count of 17,600, with 76 per cent neutrophils, 20 per cent stab forms, 3 per cent lymphocytes and 1 per cent monocytes. The sedimentation rate (Wintrobe method) was 66 mm. per hour. The color index was 0.94, and the mean corpuscular volume of the red blood cells was 86 cubic microns. Blood Kahn and Wassermann tests were negative. *Staphylococcus aureus* was demonstrated in each of 3 blood cultures. The prothrombin time (Quick method) was over 1 minute (normal, 11-12 seconds); the serum bilirubin was 4.2 mg. per 100 ml., and the thymol turbidity 7.4 units. Cephalin flocculation was negative at 48 hours. The serum cholesterol amounted to 232 mg. per 100 ml., with 72 per cent esters. The serum albumin was 0.8 gm., and the serum globulin 9.0 gm. per 100 ml., of which 7.2 gm. was gamma globulin. Three days later the values were 0.5 gm. per 100 ml. for albumin and 15.5 gm. for globulin. The protein pattern obtained by paper electrophoresis is depicted in Figure 4. The L. E. test was strongly positive (Fig. 5).

The blood urea nitrogen was 35 mg., the calcium 8.2 mg., the phosphorus 5.2 mg., and the uric acid 6.2 mg. per 100 ml. The carbon dioxide combining power was 11.2 milliequiv., the sodium 138 milliequiv., and the potassium 5.8 milliequiv. per liter.

The test for a circulating anticoagulant in the serum was negative. The direct Coombs test was strongly positive. Bone-marrow aspiration showed a normal pattern except for a moderate increase in plasma cells.

Examination of the spinal fluid revealed no cells. The protein was 108 mg., the chloride 695 mg., and the glucose 61 mg. per 100 ml.

The electrocardiogram was considered consistent with acute pericarditis or myocarditis.

The patient responded transitorily to the administration of intravenous hydrocortisone, but 24 hours later the coma deepened. She died on the 7th hospital day. Autopsy showed a subacute hepatic necrosis with cirrhosis, the liver weighing 850 gm., and the spleen 250 gm. (Fig. 6). There were multiple abscesses in the lungs, heart, kidneys and adrenal glands, as well as "bile nephrosis," acute fibrinopurulent pericarditis, old adhesive pleuritis, pulmonary edema, ascites and esophageal varices. Furthermore, massive gastric, as well as subepicardial, subendocardial and subpleural hemorrhages were noted. No histologic evidence consistent with lupus erythematosus could be found.

TABLE 1 *(Concluded).*

DATE	SERUM GLOBULIN		ALKALINE PHOSPHATASE		SERUM CHOLESTEROL	CHOLESTEROL ESTERS	UROBILINOGEN		PROTHROMBIN TIME	
	NORMAL VALUE	PATIENT'S VALUE	NORMAL VALUE	PATIENT'S VALUE	PATIENT'S VALUE	PATIENT'S VALUE	NORMAL VALUE	PATIENT'S VALUE	NORMAL VALUE	PATIENT'S VALUE
	gm./100 ml.	*gm./100 ml.*	*Bodansky units*	*Bodansky units*	*mg./100 ml.*	*%*	*Ehrlich units*	*Ehrlich units*	*sec.*	*sec.*
6/11/54	1.5 - 3.0	6.0	2.0 - 4.5	9.1	—	—	1	0.3	12 - 13	23
6/28/54		5.5		14.7	—	—		—		23
8/3/54		5.8		15.3	—	—		1.13		21
9/2/54		4.5		12.0	—	—		—		18
10/18/54		4.3		10.3	206	66.9		—		16
11/23/54		3.4		15.1	—	—		—		—
3/8/55		3.3		12.0	—	—		2.5		17
6/1/55		3.7		12.3	—	—		—		—

DISCUSSION

The detection of a positive L. E.-cell phenomenon in established liver disease lends itself to several in-

terpretations. In view of the high specificity of the phenomenon, the possibility of two independent diseases in a single patient must be considered. Moreover, the severe hepatic disturbance may be an unusual manifestation of systemic lupus erythematosus. Finally, a "biologic" false-positive L. E. test may be encountered in some patients with liver disease.

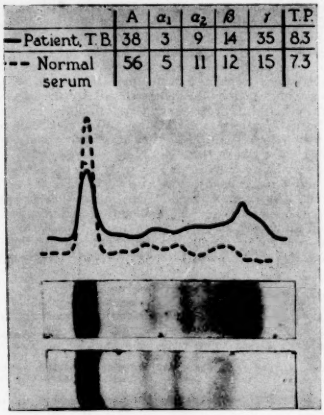

FIGURE 1. *Electrophoretic Pattern of the Serum in Case 1 (Upper Strip), As Compared with the Normal Pattern (Lower Strip).*

In Case 2 unequivocal postnecrotic cirrhosis, with subacute necrosis, was found at autopsy. This histologic pattern and the marked hyperglobulinemia were characteristic of the type of cirrhosis that has been variously referred to as subacute hepatic necrosis,[23,24] postnecrotic cirrhosis,[25] subchronic atrophy of the liver,[26] posthepatitis cirrhosis,[24] subacute yellow atrophy[27,28] and chronic hepatitis.[19] The occurrence of pericarditis and a positive Coombs test could be interpreted as features of systemic lupus erythematosus. Nevertheless, an extremely careful search in the Department of Pathology of Michael Reese Hospital (by Dr. Otto Saphir) yielded no histologic evidence of the disease. The brief period of treatment with cortisone may conceivably have obliterated all evidence of the disease, but this is unlikely.

That such severe liver damage may be a manifestation of lupus erythematosus also seems unlikely. Although some hepatomegaly is not unusual in this disease, its occurrence varying from 12 to 44 per cent,[29-31] histologic and functional abnormalities are usually minimal.[2,3,31,32] Griffiths and Vural[31] found slight to moderate fatty metamorphosis of the liver in 6 of 18 patients who had died of systemic lupus erythematosus. Mild necrosis of liver cells was found in only 1. Dubois[2] demonstrated arteritis in the liver of 1 of 62 patients. Jaundice associated with elevation of the direct-reacting serum bilirubin is rare. If present, it may be related to another pathologic process, as reported in 1 of the patients of Harvey et al.,[3] in whom the hyperbilirubinemia was considered to be caused by miliary tubercles found in the liver at autopsy. Only mild histologic alterations of the hepatic parenchyma were found in 11 cases (5 biopsies and 6 autopsies) by Kofman, Johnson and Zimmerman.[32] These consisted of areas of focal necrosis, lymphocytic infiltrations of the portal regions and slight to moderate fatty metamorphosis. These investigators considered the pattern of hepatic dysfunction in systemic lupus erythematosus to be related to the abnormal plasma proteins rather than to abnormalities of the hepatic parenchyma.

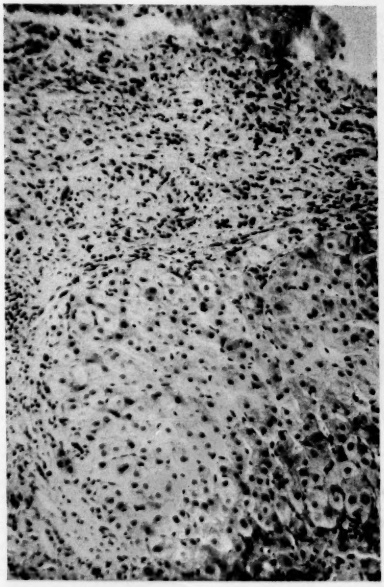

FIGURE 2. *Liver Biopsy in Case 1.*

Thus, it seems very unlikely that the patient discussed above had systemic lupus erythematosus in addition to cirrhosis and even more unlikely that she had lupus erythematosus as a *cause* of the liver disease.

In Case 1 cirrhosis of the liver was proved by needle biopsy (Fig. 2). It is of interest that the biopsy specimen obtained three months after admission revealed a pattern consistent with postnecrotic rather than with the expected Laënnec cirrhosis. It is recognized, however, that differentiation of these two conditions

is, at times, difficult, particularly by biopsy. The positive L. E. test was demonstrated in this patient during a systematic study of the relation of drug hypersensitivity to nucleophagocytosis and the L. E.-cell phenomenon.[17] The diagnosis of coincident lupus erythematosus seemed very unlikely in the absence of other supporting clinical and laboratory data.

The possibility was considered that the daily injection of crude liver extract produced L. E. cells as a manifestation of hypersensitivity. The lack of any other evidence of drug hypersensitivity, as well as the persistence of the L. E.-cell phenomenon, militates against this interpretation. An attempt to produce the phenomenon in the rabbit and guinea pig by daily injections of liver extract was also unsuccessful.[34] Only complement-fixing antiliver antibodies could be demonstrated in the serum of such animals.[34]

FIGURE 3. *Positive L. E. Test in Case 1.*

It has been postulated that autoantibodies are responsible for the continuous necrotizing activity in chronic hepatitis.[23,33] The hypergammaglobulinemia and the associated plasma-cell proliferation could be interpreted as an expression of excessive antibody production. Whether or not the presence of the L. E. factor also reflects such an altered immunologic state remains to be elucidated. Studies of the possible interrelation of antiliver antibodies, antileukocyte antibodies and the L. E. factor are in progress.[34] Joske and King[19] have suggested that the L. E.-cell phenomenon indicates the presence of autoantibodies to white cells. These authors postulate that such an immune response may also occur in diseases besides systemic lupus erythematosus that are associated with hyperglobulinemia.

The infrequency of the L. E.-cell phenomenon in

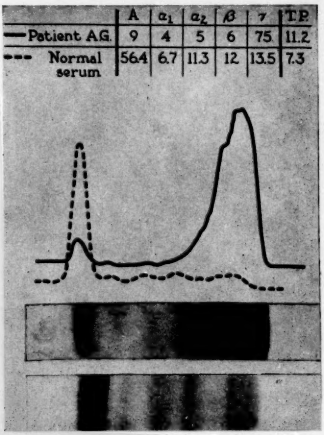

FIGURE 4. *Electrophoretic Pattern of the Serum in Case 2 (Upper Strip), Showing the High, Broad Peak of the Gamma-Globulin Fraction, As Compared with the Normal Pattern (Lower Strip).*

patients with cirrhosis is suggested by the small number of reported cases.[19-21] Sherlock[21] mentions observations of L. E. cells in young females exhibiting an unusual type of cirrhosis of the liver associated with apparent adrenocortical overactivity. Joske and King[19] describe 2 female patients with chronic active hepatitis who showed the L. E.-cell phenomenon.

TABLE 2. *Negative L.E. Tests in 56 Patients with Liver Disease.*

DIAGNOSIS		NO. OF PATIENTS
Hepatitis		11
Cirrhosis		45
Laënnec	33	
Postnecrotic	5	
Mixed	7	

Oliver-Pascual[22] refers to the occurrence of the clinical features of lupus erythematosus in a patient with cirrhosis. Hoffbauer[35] states that he also has observed the L. E.-cell phenomenon intermittently in 2 female patients with probable postnecrotic cirrhosis. Bettley[20] reports the L. E.-cell phenomenon in a fifty-year-old

man with fatal active chronic viral hepatitis, hypergammaglobulinemia and "diffuse" plasma-cell infiltrations of the bone marrow. The 2 patients described above showed histologic features of postnecrotic cirrhosis although 1 had an alcoholic background.

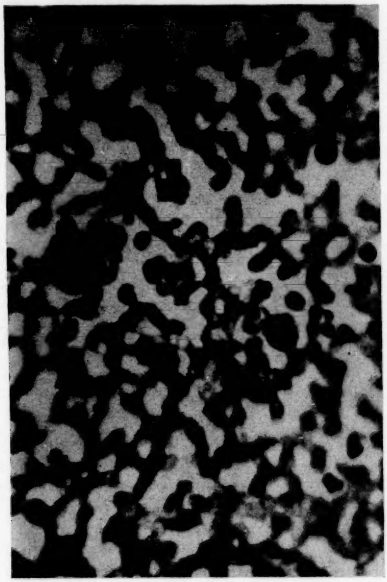

FIGURE 5. *Positive L. E. Test in Case 2.*

In a systematic study of 60 patients with acute and chronic hepatic disease (Table 2) no other example of a positive L. E.-cell phenomenon was observed.

The lack of evidence of systemic lupus erythematosus in these 2 patients, as well as the unlikelihood that lupus erythematosus could produce such a marked degree of liver disease, suggests that the L. E.-cell phenomenon in these patients represents a false-positive test. This may have an immunologic basis, an interpretation that is supported by previous observations in hypersensitivity states.[11,12,17] The presence of the L. E. plasma factor in diseases other than lupus erythematosus justifies the concept of the "biologic false-positive" L. E.-cell phenomenon.

SUMMARY

The L. E.-cell phenomenon occurred in 2 patients with postnecrotic cirrhosis. In neither patient could systemic lupus erythematosus be demonstrated.

The evidence that the appearance of L. E. cells in these patients represented neither hepatic cirrhosis complicated by systemic lupus erythematosus nor the latter with unusual hepatic complications, but a "biologic false-positive" L. E. test occurring in hepatic disease, is discussed.

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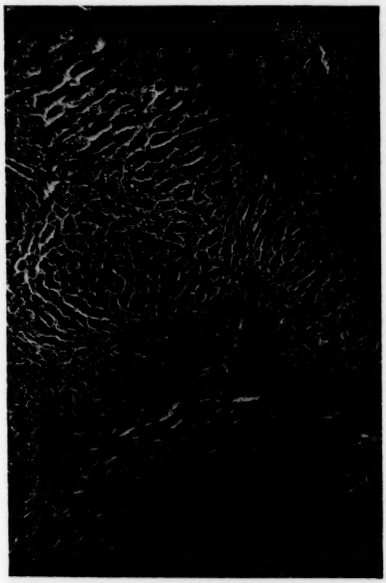

FIGURE 6. *Photomicrograph of the Liver at Autopsy in Case 2, Showing the Typical Picture of Subacute Hepatic Necrosis.*

The small degree of fatty metamorphosis is occasionally seen in this disease.

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URTICARIA PIGMENTOSA AS A PROBLEM IN DIAGNOSIS*

Report of Two Cases, One with Systemic Involvement

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THE syndrome of urticaria pigmentosa is one of the rarities encountered in pediatric practice. Patients with this syndrome are frequently seen by several physicians before the diagnosis is made. The following report of 2 such cases emphasizes several aspects of the clinical picture that may lead to the diagnosis. A brief consideration of what is now known of the metabolic anomaly is also presented.

Case Reports

Case 1. P.D., a 17-month-old boy, was referred to the Hôpital Sainte-Justine for investigation of a skin rash. He had been born at full term, with a birth weight of 2.8 kg. (6¼ pounds). There was no history of diseases in the first 3 months of life. There was no family history of skin rashes or other relevant pathologic states. The father, 32 years of age, and the mother, 34 years of age, were in good health. A brother, 3 years of age, was living and well.

At the age of 3 months the patient had been hospitalized elsewhere for "disseminated ecchymoses." Information from the other hospital revealed that the red-cell and white-cell counts, smear, hemoglobin, bleeding time, coagulation time (Lee–White method) and clot retraction had all been within normal limits. No definite diagnosis was made, and he was discharged. He was again hospitalized elsewhere at the age of 5 months. The same widespread "ecchymotic" lesions were again noted, and at that time the tip of the spleen could be felt. A hematologic investigation, including bleeding time, coagulation time, prothrombin time and bone-marrow aspiration, gave normal results except for a low-normal count of blood platelets (110,000 to 125,000 per cubic millimeter) and eosinophilia (counts that fluctuated between 4 and 22 per cent). He was believed to have thrombocytopenic purpura, and splenectomy was considered. A hematologic consultant was of the opinion that the skin lesions were not ecchymoses of hemorrhagic origin and suggested that they were a manifestation of some dermatologic syndrome. A biopsy of one of the lesions was made, and the tissue was stained by the routine technic (hematoxylin and eosin). The following histologic description was noted:

> Normal epidermis. The dermis and hypodermis are regular and without any inflammatory infiltration. The capillaries of the dermis are moderately dilated.

The possibility of vascular purpura was raised by the attending physician, and the patient was referred to the Hôpital Sainte-Justine for additional observation.

Physical examination revealed a child weighing 10.9 kg. (24 pounds) who appeared to be in good health. Except for the skin lesions described below, the physical examination was completely negative. The spleen could not be felt. Brownish-yellow macules and papules were scattered over the skin surfaces of the entire body. These lesions were irregular in shape, did not blanch on pressure and varied between 0.25 cm. and 2.5 cm. in diameter (Fig. 1). When the edge of a tongue depressor was scraped back and forth over such a lesion, a wheal surrounded by an erythematous zone at the site of each lesion developed in a minute or 2. The photograph shows such wheals in the skin lesions of the right flank (Fig. 1).

Hematologic investigation showed a red-cell count of 4,250,000, with a hemoglobin of 12 gm. per 100 ml., and a white-cell count of 9600, with 62 per cent lymphocytes, 26 per cent neutrophils, 11 per cent eosinophils and 1 per cent monocytes. Routine examination of the urine for microscopical findings, sugar and albumin was negative.

The finding of the pathognomonic urticarial wheals after mechanical irritation of the lesions, together with the general appearance of the pigmented lesions, and the age at onset left little doubt that the diagnosis was urticaria pigmentosa. The patient was discharged to be followed as an outpatient.

Case 2. M.A. (S.M.H. 92963) was first admitted to the Syracuse Memorial Hospital at the age of 9 months because of a rash since 2 months of age. He had been born in this hospital at full term after a normal pregnancy and weighed 2.7 kg. (6 pounds) at birth. There was also an apparently normal fraternal twin, weighing 3.6 kg. (8 pounds). The

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patient was nursed for 1 month and then placed on an evaporated-milk formula. At 2 months of age a generalized, erythematous macular rash, characterized by itching, developed. There was concomitant severe dermatographia. Because of the itching, many of the lesions became excoriated and secondarily infected. At the age of 9 months he was admitted to this hospital, where the physical findings mentioned above were noted. There were generalized multiple, macular, reddish lesions, more numerous over the hands, legs, sides of the trunk and abdomen. The liver and spleen were not palpable. Hematologic investigation revealed a red-cell count of 4,100,000, with a hemoglobin of 8.7 gm. per 100 ml. and a hematocrit of 31 per cent, and a white-cell count of 20,300. The smear was hypochromic and microcytic. Routine urinalysis was negative. A dermatologic consultant stated that he could not make a diagnosis and recommended a biopsy. One of the lesions of the left flank was biopsied and the section stained with hematoxylin and eosin. The histologic report was as follows:

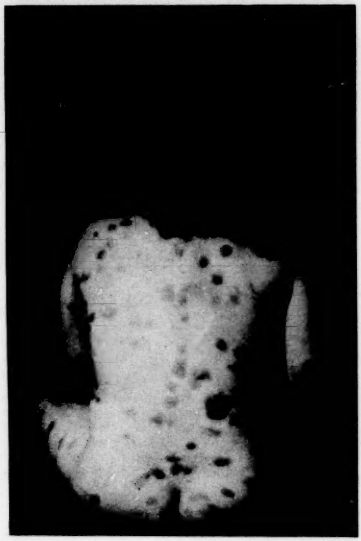

FIGURE 1. *Appearance of the Skin Lesions in Case 1.*

> Sections show multiple nests of cells arranged in the dermis much like those of a pigmented nevus; however, each of the cells is isolated and sharply outlined. They may be histiocytes, but there is very little vacuolization such as would be present with lipid deposit.

No definite diagnosis was established, and the patient was discharged to the care of his family physician. He was taken to several dermatologists, who regarded this as an allergic reaction. Attempts to perform skin tests resulted in a severe reaction. There was no family history of allergy, and he had had no evidence of asthma or hay fever.

During the first 2 or 3 years of life it became apparent that he bled excessively after trauma. One scalp laceration required pressure for 3 days to control the bleeding. At 5 years of age he was readmitted to this hospital because of the development of hepatosplenomegaly and "stomach ache." He appeared chronically ill, with moderately retarded growth. His skin was covered with a pale, erythematous rash, more marked on extremities. There was severe dermatographia. The liver edge was 3 or 4 fingerbreadths below the right costal margin, and the spleen was greatly enlarged, so that it came to within 1 fingerbreadth of the left iliac crest. The spleen had a firm, sharp edge. A hematologic investigation by Drs. William Waters and Willet Bowen revealed the presence of mast cells in the bone marrow and peripheral blood. When the skin-biopsy tissue taken 4 years previously was restained by the Giemsa technic, the mast-cell proliferation was quite evident. Figure 2 shows the appearance of lymph-node-biopsy tissue in this case on staining with hematoxylin and eosin, as contrasted with Figure 3, which shows the same tissue stained with the Giemsa technic.

DISCUSSION

The 2 cases of urticaria pigmentosa presented above illustrate some of the pitfalls in the path of the proper diagnosis of this syndrome. In both, the first pathological examination of skin-biopsy material did not reveal the diagnosis, owing to the inadequacy of the hematoxylin and eosin stain in demonstrating mast cells. In Case 1 the skin lesions were at first mistaken for hemorrhagic purpura. The pathognomonic urticarial wheal produced by irritation at the site of a skin lesion finally gave the clue to the diagnosis. Case 2 was taken to be a xanthomatosis or dermatitis of unknown origin until the combination of generalized skin lesions, urticaria and dermatographia was recognized as a diagnostic entity and mast cells were found in the blood and bone marrow.

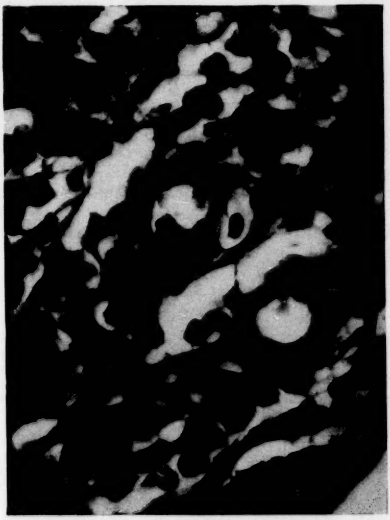

FIGURE 2. *Histologic Section of a Lymph Node in Case 2 (Hematoxylin and Eosin Stain X 790).*

Mast cells have been found to be associated with skin pigmentation and with several chemically identi-

fiable substances: hyaluronic acid, histamine and heparin. Asboe-Hansen[1] has reviewed the evidence supporting the concept that hyaluronic acid is formed by the mast cells. A parallelism between pigmentation of the skin and excessive accumulation of mast cells in the skin has been described by Woringer[2] in certain pathologic states. Previous studies have indicated that mast cells contain extraordinary concentrations of heparin and of histamine.[3-7] The evidence is very strong that the histamine of mast cells is present in the metachromatic granules of these cells.[5-8] It has been hypothesized that the organic acid heparin is the basophilic material of the mast-cell granules, and that histamine is the organic base with which the heparin is associated.[8]

Figure 4 presents some of these concepts diagrammatically. The symbol H-B refers to the bonding between heparin and the basophilic stain that results in the optically visible granules of the mast cell. The symbol H-H′ refers to the bonding between heparin and histamine that is believed to occur normally in

FIGURE 3. *Histologic Section of a Lymph Node in Case 2 (Giemsa Stain X 790).*
Note the striking demonstration of granules in mast cells provided by this stain.

mast cells. The symbol H-P refers to bonding between heparin and an organic base such as protamine that may also occur under some conditions.

It is possible that there is an etiologic connection between the urticarial reactions and the dermatographia in urticaria pigmentosa and the histamine or histaminelike substance in the hyperplastic mast cells. Grupper[9] has demonstrated that the administration of antihistaminic substances does not prevent the pathognomonic urticarial wheal that follows the local irritation of a skin lesion. This suggests either that the histamine concept is not the whole explanation or that the antihistamine could not reach the histaminelike substance to inactivate it. Grupper and Brux[10] have reported that a properly stained skin biopsy will

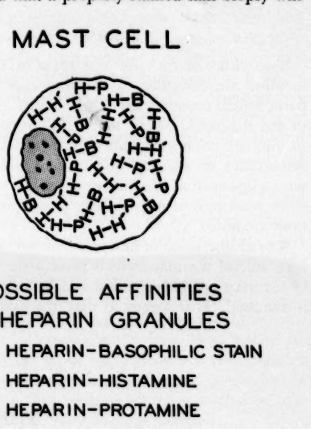

FIGURE 4. *Schematic Representation of the Mast Cell and Its Heparin Granules.*
The symbols H-B, H-H′ and H-P indicate chemical bonding of mast-cell heparin with basophilic stain, histamine or protamine respectively.

show three or four times more mast cells if the skin lesion has been previously irritated. On the basis of the schema presented in Figure 4, one could also postulate that the discharge of histamine or histaminelike substances by these cells might disrupt the heparin-histamine bond and make available more positions for the union between heparin and the basophilic stain.

Bloom[11] has reported striking gross and microscopical regression of multiple mast-cell tumors in a dog, in association with cortisone treatment. Although the etiologic mechanisms may not be the same in the canine and human states, carefully controlled therapeutic trials with cortisone or hydrocortisone appear to be indicated in human urticaria pigmentosa.

Riley and West[5] found increased histamine content in skin from a patient with urticaria pigmentosa. Estimation of histamine concentration in liver tissue in Case 2 revealed enormously elevated values (over 1,000 microgm. per gm.).[12,13] Estimation of heparin-like material in the liver tissue of Case 2 has also revealed greatly increased concentrations.[14] It seems

most likely that the metabolic error in urticaria pigmentosa is congenital inadequacy of an enzyme involved in the degradation of histamine or of heparin. There are at present no data to indicate whether the enzymatic defect is primary to the intermediary catabolism of histamine or of heparin. The proliferation of mast cells may be a homeostatic reaction to provide an intracellular "storage" place for these compounds, which are so potent when free in plasma.

Summary

Two children with the syndrome of urticaria pigmentosa are described. In neither case did the first pathological examination of skin-biopsy material assist in the diagnosis, owing to the failure of the hematoxylin and eosin stain to demonstrate mast cells. The importance of staining this type of biopsy material with a dye such as Giemsa, which is known to demonstrate mast cells, is emphasized. Other pitfalls of diagnosis are noted.

A brief discussion of newer knowledge of the physiologic role of the mast cells is presented. The relation of the mast cell to histamine and heparin metabolism is discussed. It is suggested that urticaria pigmentosa is a congenital metabolic error of histamine or heparin metabolism, and that the mast-cell proliferation is a phenomenon secondary to this.

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SPECIAL ARTICLE

THE "SKID ROW" PROBLEM

Further Observations on a Group of Alcoholic Patients, with Emphasis on Interpersonal Relations and the Therapeutic Approach

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IT is the aim of this paper to discuss psychiatric observations made over a three-year period of 101 destitute and homeless alcoholic men, a group hitherto inaccessible to such exploration. The rehabilitation program[1] of the Long Island Hospital of Boston, Massachusetts, afforded a psychiatric and medical team the opportunity to study these men both in and out of the hospital.

That such a group of men, coming from the Skid Row section of the city, represents the most debilitated type of alcoholic patient is a matter of common observation, although Straus and McCarthy[2] differentiate such patients from the true addictive drinkers. That these men suffer a profound personality disturbance, however, as manifest in their interpersonal relations, has received little attention. This striking failure in their interpersonal relations needs special emphasis because it is essential to an understanding of the isolated lives of these men and the setup of any rehabilitation program for them. The theme of this failure may be briefly stated. In the give-and-take of normal human relations, these men cannot *give*: they can only *take* from a supplier or protector, who is usually a woman. She is "loved" only so far as she tries to fulfill their insatiable demands. Sooner or later, the man in this group loses this person and, unable to form a new relation, sinks into the pattern of the Skid Row life. To explain this failure the history and drinking habits of these men and their struggle to restore themselves to their families after they have given up alcohol are discussed below in detail.

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Social Data

The majority of the men in this study were in the middle forties, with 13 in the thirties and 23 over fifty. Except for 3 who were from the middle class, all came from lower economic groups. Ten were Protestants of Scandinavian or English descent. The

remaining 91 were Roman Catholics who, with the exception of 3, were second generation Irish-Americans. Fifty men had achieved a partial high-school education, and another 50 completed at least grammar school. One man was a college graduate who had long since abandoned his profession as a teacher. Thirty-five men were skilled workers; the rest had no trade. In general, they had for years either been unemployed or worked at such marginal jobs as dishwashers, porters, gardeners' assistants, and temporary railroad laborers.

This relatively large number of Irish Catholics merits a brief comment. It is well known that this group comprises a large segment of the Boston population, roughly estimated at about 70 per cent, and many of them in the lower income bracket. Other investigators, such as Haggard and Jellinek[3] and Kirby[4] have demonstrated the high prevalence of alcoholism among Irish-Americans, so that the high percentage found in the Long Island Hospital group is not surprising. Of equal significance is the very low prevalence of alcoholic patients among minority groups. Thus, in the five years during which this program has been in operation, only 1 Jew, 1 Negro, and 2 Italian-Americans have volunteered for help. It is difficult to explain why so few of them are seen at the hospital, except on the basis of a number of cultural factors, which have been carefully studied by Snyder,[5] Williams and Straus,[6] Glad[7] and others.

The Skid Row Community

With few exceptions, each man came to the hospital from the same section of the city, and each life pattern showed a surprising similarity to the others. Devoid of any family life, they dwelt in the Dover Street area, characterized by its elevated railroad, pawn shops, taverns and run-down rooming houses where rent is cheap. Except for the illusory companionship within the tavern, or a rare and meaningless sexual affair, they lived as isolated a life as one can live in a large city.

Driven together in large numbers through economic necessity, these men formed a kind of community of the isolated, of which the uniting features were drinking and destitution. This community, known as Skid Row, makes a widely felt impact on the rest of the city. For example, over a ten-year period, the 101 men of this group spent, on an average, a quarter of their time, representing over *40,000* days, either in jails or in other public institutions. Forty-nine marriages were dissolved, so that 49 wives and 76 children became dependent on city agencies or charitable organizations. Such social facts as these, as well as other problems created by the drinking habits and poverty of these men, make the "community" to which they belong a chaotic one.

The drinking habits marked the end point of more than two decades of serious drinking. All but 10 of the group stated that they had begun to drink in their early twenties. These 10 men claimed a drinking problem early in adolescence. By their early thirties, most of them realized that their drinking was exceedingly heavy, but thought that they "could handle it," meaning that drinking had not yet interfered with their ability to hold a job. In the next ten years, however, there was a steady decline and estrangement from their families. This period was crucial, for up to this point most of the men had maintained a relation to someone, usually a mother or a wife, who for years, willingly or unwillingly, had given in to them by providing the money with which to buy alcohol or protecting them whenever they were in trouble. When their protectors left them or died, their life of isolation really began. Unable to find a substitute, they "joined" the community of Skid Row.

Of the 101 men, 49 became inhabitants of Skid Row when their wives left them on a permanent basis. Thirty-three joined when their mothers died. Only 8 gave up the ties to the family early in their drinking careers. Another interesting group of 10 represented the most isolated of all. This group, except for brief jaunts into orphanages, foster homes or marriages, might be considered to have been native inhabitants of Skid Row, for, having lost their families very early in life, they had acclimated themselves to this area when they were as young as twelve or thirteen, years before they became alcoholic.

With the loss of their family relations, for whatever reason, these helpless men had to turn to the community for their providers and protectors and unconsciously became dependent on three figures — the bartender, the policeman and the employer. The bartender became the supplier who asked no questions and demanded only money. The policeman unwittingly became a "mother" substitute when he threw the helpless drunks into jail, without which protection their very lives would have been in jeopardy. The employer represented their only "normal" relation, and to him at least they gave of themselves in sporadic bursts of energy. Generally speaking, although they tended to be good workers, they were unreliable, because as soon as they earned enough money, they were off to the tavern. Thus, their ability to give, even in the work situation, was limited to whatever time they needed to earn enough money to satisfy, as ever, their own gratification.

Many men maintained themselves by these sporadic jobs for a long period but ultimately lost their ability to work and hence their ability to earn money. This loss brought about their final separation from society and a complete isolation. As a result, a furious pitch of uncontrolled drinking ensued, called by them "out on the stem." No longer did they need to hold themselves responsible to anybody for anything; they were now free to use all their energy, ingenuity and

resources to obtain alcohol in any form. Once free from external controls, such as work and family, they were also free from the inner controls of conscience, ideals and values. To get money for alcohol, they begged, borrowed or stole without qualm, and even a once devout churchgoer stole from the poor box.

This was the time when, in their destitution, bay rum, vanilla extract and muscatel were luxuries. For the hardy, even rubbing alcohol could be used if taken with crackers or grass to prevent vomiting. On a Sunday, when the stores were closed, Sterno ("canned heat") served as a source of supply for these desperate men. The preparation of the drink was often a group project, with the steadiest hand performing the intricate operation in stolen empty milk bottles. So shaky and tremulous were the men that the steadiest had also the duty of bottle feeding his companions, one by one.

The Personality Disorder

Table 1 shows the diagnostic classification of the group under discussion.

Table 1. *Diagnostic Classification.*

Diagnosis	No. of Cases
Personality-trait disorders, passive-aggressive type	55
Borderline schizophrenia	23
Schizophrenia, overt (ambulatory)	6
Sociopathic personality, dissocial reaction	7
Undiagnosed	10
Total	101

The proportion in each diagnostic classification differs somewhat from the Skid Row group of an incarcerated workhouse population described by Feeney et al.[8] These authors reported a higher proportion of psychotic patients and those with organic brain disease, whereas at the Long Island Hospital such patients were eliminated from the program at the outset. The protective nature of the hospital certainly attracts large numbers of men with strong dependency yearnings that characterize the passive-aggressive type. It is probable, however, that the workhouse group is more typical of the Skid Row population at large. At any rate, it seems clear that selection of patients plays a large part in explaining the diagnostic differences between groups.

Whatever the diagnostic classification, these men showed unusually regressed and primitive relations, which have been described in detail by Bergler,[9] Knight[10] and Glover.[11] This relation was a simple one in which they were interested only in those who gave them their supplies, whether alcohol or money. It was on the basis of the demanding quality of their personality structure that they differentiated friend from enemy. Those who gave or supplied were "friends," but only as long as they gave in to the demands. As soon as the friends began to refuse the demands made of them, they were regarded as enemies. Since the desires were insatiable, these alcoholic men finally succeeded in alienating everyone. It was only when exhausted, ill and destitute, that they were at last forced to seek the protection of either the jail or the hospital.

With his enforced sobriety, each man had to reckon with the problem of his isolation, either by facing an utterly empty and futile life, or by denying its existence. If he faced his loneliness and his self-inflicted failures, he suffered so intense a depression that upon release he drank himself into a numbing stupor. If he denied his problem, as most did, he created a situation just as grave — that is, he could not see his deficits but assumed instead an air of irritating pseudoconfidence, which left him free to turn his back on the help he desperately needed, only to suffer the anxiety of being completely isolated within the lonely four walls of his dingy room. This, in turn, drove him back to the tavern. Thus, this group of alcoholics seemed to be caught in a vicious circle, the end point of decades of drinking: the more they drank, the more isolated they became; the more isolated they became, the more they drank.

Therapeutic Approach

To break into this pattern, an active rehabilitation program was organized at the Long Island Hospital. The program, in operation since 1951, functioned as follows:

The base of operations was a large city hospital that, among other facilities, had a 300-bed dormitory unit where these men could reside. Here they volunteered for the program, which was so arranged that the men lived in the dormitory and worked in the community for an indefinite period. All the men, with few exceptions, were placed on tetraethylthiuram disulfide (Antabuse).[12] It was possible to carry as many as 70 men at a time on the program. After the men left the hospital, they were offered the use of an evening clinic in the city proper, which served to help them through their difficult readjustment to the community. From the onset of the program, there was indispensable co-operation with such community facilities as the United States Employment Agency, church organizations, Alcoholics Anonymous and the courts. In short, the program operated as a community venture that attempted to meet the physical and emotional needs of these men.

It was fortunate that the rehabilitation program could offer this group partial protection[13] in the form of food, shelter and work. Equally important, it was possible to create "group spirit," a positive force with which they could identify. Through this identification, their isolation tended to be alleviated. During this period of partial protection, which often lasted

for months, they found it relatively easy to give up liquor. It was rare for any of them to break the rule of no drinking on the hospital grounds. Sooner or later, the pressure of loneliness motivated them to try to restore themselves to the remaining members of their families. This attempted restoration demonstrated again the alcoholic patient's own failure in his human relations. Denying his inadequacies, the passage of time and other factors such as divorce, he still expected love and devotion from those who had loved him previously. He fell immediately into his former pattern of "all take and no give." His unreasonableness led to the inevitable rejection, the one thing he could not tolerate or understand. This rejection frequently became his rationalization for drinking again.

An example of this was a man who, having been separated from his wife for five years, returned to her after a few months of sobriety, confident that she would cater to all his desires. She, however, had learned to love her freedom. When she balked, he became furiously indignant, accusing her of not being a woman; that all women of today were no good; that his mother (*sic!*) surely would have been different and would have given him what he wanted. He could not see how he had failed his wife in every respect and that in the five intervening years she had learned how to live for herself. Significantly, he repeated this frustrating experience three times before finally giving her up.

Another man tried to live with his daughter, whom he had not seen for years. After returning to the hospital, he stormed self-righteously that his daughter was an ingrate and that she had no respect for her father because she not only refused to turn over to him the money she had earned but also refused to obey his rigid restrictions regarding her social life. That he never had done anything to earn her respect and that the passage of time had changed his little girl to a grown woman, he could not comprehend.

Still another man, who knew his ex-wife had remarried, confronted her one day with the fact that he had been sober for six months and therefore demanded that she return to him. Upon her refusal, he was grievously shocked and disappointed, claiming that she had broken her promise to return (a promise made ten years previously).

The failure of these alcoholic men was thus not only in their drinking but also in their total inability to view their interpersonal situations as reasonable men. Once the alcoholic patient had lost his protector, he searched in vain for someone to supply his insatiable needs. Since no one could fulfill this role, and since he denied any responsibility for his plight, he was destined to meet only rejection from other people. It might take many hard knocks before he was willing to concede to his own lacks and try to do something more constructive about them.

Results

That the problem is not completely hopeless is indicated by the fact that 12 men of the group found a solution. They not only renounced alcohol completely for three years but also restored themselves to their families. One man married the widow of his alcoholic brother; after a stormy and aggressive courtship, he rescued her from destitution, as well as from her own alcoholic tendencies. Three men conceded the loss of their wives and went back to their original families. Five men lived with their married daughters. One man finally married after sixteen years of courtship. It is significant that only 1 man out of 49 was able to re-establish himself with his wife. Those who lived with their married daughters seemed to lead the most satisfactory lives. Here, they could be grandfathers, playing with their grandchildren without assuming much responsibility. In this situation, not much was expected of them, and they learned to give more willingly. Indeed, a crisis brought about a dramatic change in one man. When his grandson became seriously stricken with meningitis, he moved in, paid for "the best of physicians" and nursed the boy through a prolonged and difficult convalescence. Thus, he re-established himself in the hearts of his children but, more important, proved to himself his own worth.

Twenty men remained sober for three years but, in contrast to the 12 mentioned above, were unable to adjust themselves outside the hospital. They made their daily trips to the city to work. Once a week they paid board, went to church and occasionally made a visit to old friends or perhaps an interested relative. Viewing the city as too dangerous for them to live in, as indeed it was, they made the hospital their home and thereby formed a small "family" of their own.

Not quite so successful were another 22 men who had drinking episodes two or three times a year. Although these episodes were severe, the men were able to stop in a comparatively brief period and returned to the hospital to begin again. Compared to their previous mode of drinking, these episodes were much less intense, and it was rarely necessary to jail them.

The attempts of these men to restore themselves into the community were unsuccessful. They repeated these rejecting experiences, examples of which have already been cited, without learning anything by them and clinging tenaciously to their denial. One man had made nine attempts to regain his wife, each unsuccessful attempt preceding a drinking experience, and still he strongly denied any responsibility for his wife's rejection or for his own drinking. Even those without families tended, characteristically, to select people who inevitably rejected them. For example, many of them were drawn to the "bar-fly"

woman who frequents the taverns and fleeces her victim after getting him to drink.

The remaining 47 in the group must be regarded as failures. After innumerable attempts, they showed only the slightest improvement in their drinking habits and made no effort to reintegrate with their families. It was the policy of the hospital not to reject these failures, because there were always one or two men who, after many unsuccessful efforts, responded well.

Goals of Therapy

By means of the rehabilitation program, 54 of this group of 101 men were able to break from their chaotic pasts. Only 12 of the 54 were able to function successfully independent of the hospital, whereas the remaining 42 men were successful only by remaining partially dependent upon the hospital. This dependency raises the question of the goals of therapy. "Cure" at the present stage of knowledge is out of the question. Social improvement, even if it implies dependency upon the hospital, is perhaps the most that can be expected as a goal of therapy for this group.

The question comes up of how to measure the degree of social improvement. This can be gauged by the drinking habits of these men and by observation of their social reintegration. It is easy to judge and classify their drinking habits in qualitative or even quantitative terms. It is more difficult, however, to estimate the degree of social reintegration. Observation of their work habits, their adjustment to the hospital, the return of religious standards and their attempts to reintegrate with their families offers important clues. In all these steps, however, the type of relation they form is of basic importance. If a man returns to his church, for example, only time will tell whether he is making a histrionic and unrealistic gesture to get his wife back, or whether he is joining because of a genuine desire to break out of his isolation by recapturing some of his long-lost values.

Discussion

The approach of the hospital then has been to accept these men as they are, with their extremely vulnerable and damaged personalities, which, as already explained, limit the goal of therapy. Avoiding complete dependency, the hospital encourages the men toward as much independence as they can tolerate, which, as the figures show, is limited. Comparison of their past and present lives, however, indicates considerable improvement and thus makes valid this new approach. In the past, these men spent a quarter of their time in jails or other public institutions, and the rest of their time drinking. They were considered so hopeless that no sustained effort at rehabilitation was made. Under the present system, the time the 54 relatively successful men spent in jail or in drinking was almost negligible. Even for the unsuccessful, there was at least hope.

With the exception of the 12 men who achieved independent lives, however, the relative success of the rest depends on their willingness to maintain a relation to the hospital. If, for whatever reason, the hospital discharged them, most of them would surely find their way back to the Skid Row life.

Judging from the experience with this group, any community that attempts to deal with these people from Skid Row has to be prepared to assume a trying and difficult responsibility. Both professional and lay members of the program must be aware of the fact that they deal with a complicated sociopsychiatric problem. The approach must be based on an understanding of the needs of these men. Catering to them is not the answer. Punishment, too, is as outdated as a strait jacket in a well run state hospital. Taking into consideration the chronic vulnerability of this group of men, those responsible for the program should realize that anything but a long-term approach with adequate facilities for follow-up care is a futile gesture.

Summary

This paper is a report based on a study of 101 destitute alcoholic patients from the Skid Row section of Boston. By and large, they originally came from the lower economic brackets and had been alcoholic for many years. With the dissolution of family ties, they slipped into the isolated life of Skid Row, from which they could not extricate themselves. Certain facets of their basic personality structure, manifested in their interpersonal relations, are emphasized. From a study of their drinking habits and their struggle to restore themselves to family ties, it appeared that they placed insatiable and impossible demands on those to whom they tried to relate. Denying their inability to *give* in their human relations, they placed themselves over and over again in situations in which only rejection could result and became enmeshed in what appeared to be an endless cycle of drinking and isolation.

To meet the physical and emotional needs of these men, the rehabilitation program of the Long Island Hospital was instituted. A three-year study indicates that whereas 54 out of 101 men showed improvement in drinking habits, only 12 were successful in restoring themselves to their families and in living independently from the hospital. These figures show the limitations of the goals of treatment, and demonstrate that one must expect that a considerable number of the men will maintain their improvement only as long as they remain partially dependent upon the hospital.

Finally, since the effect of this group of alcoholic men was so widespread as to involve the entire community, it is suggested that any program, to be effective, requires the co-operation of diverse community resources.

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MEDICAL PROGRESS

SYPHILIS AND ITS MANAGEMENT (Concluded)

A Present-Day Problem

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Physical Examination

The objective is to find evidence of present or past syphilis in any stage, either of congenital or of acquired disease. The following are some of the more common objective findings, with brief interpretations:

Head and face. Deformities here are prominent in patients with congenital syphilis. While taking the history, the physician has ample opportunity to observe the patient's features. He should look for the facies of congenital syphilis, with bulging frontal bosses (Parrot's nodes), "saddleback" nose, rhagades at the angles of the mouth and radiating scars at the corners of the eyes, and for the concave face with short maxilla and protruding mandible.

Is there a forward and backward jerking of the head that is synchronous with the heart beat? This is frequently found with aortic insufficiency (de Musset's sign).

The hair should be inspected for alopecia, particularly the motheaten type characteristic of secondary syphilis. Chronic nodules of the scalp or forehead, particularly at the hairline, may be gummas.

Eyes. Small, unequal pupils that fail to respond to light but react to accommodation (Argyll–Robertson pupils) are present with cerebrospinal syphilis. Paralysis of the extraocular muscles may indicate chronic meningovascular syphilis. One should look for evidence of interstitial keratitis and iritis and examine the eye grounds for signs of chorioretinitis; the optic disks should also be studied.

Nose and mouth. In addition to the saddle deformity of the nose, one may have a painless perforation of the nose or a painless thickening of the septum. The upper lip is a commoner site of extragenital chancres than the lower lip, particularly in the female.

The teeth should be carefully examined. Hutchinson's triad of late congenital syphilis, described in 1861, consists of interstitial keratitis, eighth-nerve deafness and changes in the teeth (Hutchinsonian teeth). Hutchinson's teeth as originally described involve the upper central incisors of the permanent teeth, but not the deciduous or "milk" teeth. The teeth are short and narrow and thick in the middle, anteroposteriorly. Instead of becoming wider as they descend from the gum, they are narrower at their free edge than at their crown; at their free edge is a deep vertical notch made by the breaking away or underdevelopment of the middle lobe of the tooth crown. This notch, together with the "screw-driver" edge of the tooth, produces the typical deformity. The first, or six-year, molars may have what appear as multiple cusps on the grinding surface; the cusps are small and deficient in enamel, and decay easily. These are called "mulberry" molars (Moon, Fornier). The upper first molar may have on its lingual aspect an accessory cusp called Carabelli tubercle. This is not a sign of congenital syphilis.

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In the mouth mucous patches and primary lesions of the tongue, tonsils and pharynx should also be looked for. In late syphilis a multilobulated tongue, with atrophy and leukoplakia, is seen. The palate may be perforated also in this stage.

Neck. In syphilitic disease of the heart with aortic insufficiency, there may be bulging and pulsating neck vessels. The carotid arteries beat with unusual force and violence. Aneurysm of the carotid artery may produce enlargement on one side of the neck. Such an expansile enlargement pulsates with the heart beat. The neck should also be examined for cervical adenopathy.

Heart. Uncomplicated aortitis may be suspected in a middle-aged patient, usually male, with a history of substernal discomfort, who also has an accentuated second aortic sound, either tambourlike or bell-like. However, hypertensive or arteriosclerotic patients may have similar heart sounds. By x-ray study and fluoroscopy, the aorta, particularly in its ascending parts, is found to be dilated. Again, hypertension and arteriosclerosis must be ruled out before an x-ray diagnosis of syphilitic aortitis can be made. The electrocardiogram offers no specific diagnostic help.

Aortic regurgitation causes hypertrophy of the left ventricle and, eventually, congestive heart failure. It is found in rheumatic endocarditis, syphilis and arteriosclerosis. Syphilitic aortic insufficiency occurs usually in males of middle age; it comes on later than aortic insufficiency of rheumatic endocarditis and earlier than that due to arteriosclerosis.[18] The diastolic aortic murmur is usually quite distinct, soft and blowing, like the sound of whispering the word "awe," wind in a cave or the phrase "Winnie the Pooh."[19] The distribution of the murmur follows the direction of the regurgitant stream — that is, downward and to the left. It may be heard at the second right intercostal space close to the sternum (Erb's point), but in many patients the murmur is often loudest along the left sternal border at the second, third and fourth ribs, or over the sternum itself. In many cases there is a concomitant systolic apical murmur with or without a diastolic Austin-Flint murmur. The systolic blood pressure is increased, with normal or low diastolic pressures that produce a wide pulse pressure, evidenced by pulsating carotid arteries in the neck and at the suprasternal notch, with a jerk of the head synchronous with each heart beat — de Musset's sign. The face is pale in contrast to the flushed cheeks of mitral stenosis. The wrist pulse is of the characteristic Corrigan or water-hammer type (described in 1832). Over the large arteries of the extremities may be heard Duroziez's murmur, which is a to-and-fro murmur, and also pistol-shot sounds. The capillary pulse of Quincke may be disclosed by gentle pressure on the fingernails or by a flashlight shone under the fingertips and observation of the alternating flush and pallor of the nail bed synchronous with the pulse. X-ray examination and fluoroscopy will reveal hypertrophy of the left ventricle, dilatation of the aorta and Corrigan's pulsation at the aortic arch. The electrocardiogram is not diagnostic.

Although most of the aneurysms of the thoracic aorta are syphilitic in origin, traumatic, arteriosclerotic and congenital aneurysms are occasionally seen.[20] The signs and symptoms will depend on the location and size. Aneurysms of the ascending aorta are usually silent. Those in the transverse and descending aorta may produce pressure on the trachea and major bronchi, causing cough; tracheal tug; hoarseness and aphonia from pressure on the recurrent laryngeal nerve; dysphagia from compression of the esophagus; difference in blood pressure in both arms; pupillary inequality from pressure on the cervical sympathetics; or pain in the chest or back from bone erosion. Because of these possible involvements, x-ray examination of the chest should be done on all patients with late as well as latent syphilis.

Syphilitic coronary-artery disease is similar in its manifestations to coronary sclerosis and should therefore be suspected in a middle-aged patient with an abnormal electrocardiogram. Patients with cardiovascular syphilis, particularly those with aortic insufficiency, have a concomitant neurosyphilis more often than not.

Lungs. Syphilis of the respiratory tract is rare. The diagnosis is usually established at autopsy or indirectly as the result of a therapeutic test with penicillin. Symptoms, if present, are persistent hoarseness, dysphagia if the epiglottis is involved and sometimes respiratory stridor. The lesions are usually nodular, noduloulcerative or gummatous, involving the larynx or bronchi. Gummas of the lungs have the same characteristics on physical examination as any mass in the lungs. The differential diagnosis rests usually between pulmonary tuberculosis, neoplasm and fungous infection. The history is one of easy fatigability, gradual and continual loss of weight, cough and hemoptysis. There is often an afternoon rise in temperature. The x-ray film may suggest a localized neoplasm or a more widespread exudative or fibrotic process. The response to penicillin in gummas of the lungs is dramatic.

Abdomen. Syphilis of the stomach is rare, and there is no specific finding on physical examination. The history suggests peptic ulcer or gastric neoplasm. By x-ray study the roentgenologist or, by gastroscopy, the physician may suspect syphilis, but the final test may be the therapeutic response to penicillin or pathological examination after surgery. There may be one or more nodules or a gummatous infiltration in the submucosa, which ulcerates and finally scars and constricts the stomach, particularly at the prepyloric end. A series of these infiltrations may result in a leather-bottle stomach (linitis plastica).

Liver and spleen. In secondary syphilis the liver is occasionally enlarged, and this is often accompanied by jaundice. In late (tertiary) syphilis, a gummatous hepatitis may be seen, characterized by an irregular enlargement of the liver on palpation. The surface may feel pebbly or nodular, and syphilitic hepar lobatum may be suspected. If the gummas are not on the surface, an enlarged and smooth liver is felt. Frequently, when the liver is enlarged there is also splenomegaly.

Because syphilitic hepatitis is rare, other causes of hepatic disease should first be considered in spite of a positive blood test. However, these cases should be treated with penicillin if all other procedures are ineffective.

Gall bladder. Strangely enough, the gall bladder is rarely involved with syphilis.

Intestines. Infrequently, the intestines are affected by gummatous infiltration. The diagnosis is made at operation or autopsy. There are no specific physical findings on palpation of the abdomen. The early symptoms are those associated with an acute enteritis, and the late ones those of an obstruction.

Kidney and bladder. The kidneys and bladder are rarely involved except in tabes dorsalis, when an atonic bladder may be found. Cystometrographic studies will confirm the diagnosis.

Uterus, ovaries and tubes. For some unexplained reason, the ovaries, tubes and uterine body are spared.

Genitalia. The primary lesion of syphilis, either single or multiple, usually occurs on the genitals. In the male it is most frequently behind the glans or on the corona. In the female the chancre may be located on the labia, in the vagina or on the cervix. The secondary lesions, consisting of moist papules, may be seen on the genitals as well as the perianal area (condylomas).

Testes. Gummatous infiltration of the testes is unilateral more often than bilateral. It may or may not involve the epididymis. The affected testicle is enlarged, hard and nontender. With contraction from scar tissue, it forms the so-called "billiard-ball" testis.

Bones and joints. The bones and joints are usually examined as part of the regional examination and not necessarily as a separate and distinct system. The long bones are more apt to be attacked by syphilis than the flat ones. Of the long bones, the tibia is more frequently involved. The skull and the clavicle, particularly at its sternal end, are the more vulnerable flat bones.

In the skull, the syphilitic process involves the outer table at first, and may spread to the inner table with extensive destruction. It may penetrate to the meninges and brain. There may be nodular lesions on the skull or localized areas of tenderness over the eroded, worm-eaten skull as viewed on the x-ray film.

On the chest, syphilis of the clavicle usually manifests itself as a nodular swelling that is hard and not painful. The nodule sometimes breaks down and ulcerates the overlying skin. It may involve the sternoclavicular joint and the sternum itself. Syphilis of the clavicle is seen in both acquired and congenital syphilis, more often in the latter (Higouménakis's sign).

The tibia when involved manifests a roughened, thickened anterior surface, so shaped as to resemble a saber. Sometimes, the surface of the tibia is pitted by holes that can be felt.

The joints may be involved in secondary syphilis and less so with primary syphilis. The patient complains of arthralgia, but physical and x-ray examination reveal nothing abnormal. In late syphilis, however, particularly in late congenital syphilis, there may be painless hydrarthrosis (chronic infusion) of the weight-bearing joints, knees (Clutton's joints, described in 1886), ankles, elbows and wrists. These infusions are more often bilateral than unilateral.

Charcot's disease, or neurogenic arthropathy (described in 1868), is often seen in tabes dorsalis, attacking especially the joints of the knees, ankles, hips, shoulders, elbows, wrists, hands and spine; they are unilateral oftener than bilateral and may involve many joints, more often only one. The pathologic changes are the result of damage to the trophic nerves of the joint. Subsequent damage is due to the lack of sensation in the joint. The onset is gradual, usually with painless swelling. The disease may progress to eventual loss of normal joint contour, enlargement of the joint, hypermobility and destruction of bone, with small broken pieces producing crepitus and a "bag-of-bones" sensation to the touch. Because of the loss of function of sensory nerves, trophic ulcers may form on pressure areas such as the sole of the foot (mal perforans), particularly at the first or fifth metatarsal-phalangeal joint.

Nervous system. The manifestations of neurosyphilis are many. All the reflexes, both deep and superficial, should be tested. Beginning with the cranial nerves, a systematic examination should be carried out. When Argyll–Robertson pupils are present, they mean neurosyphilis. They are rarely encountered in other neurologic conditions. They are most often seen with tabes dorsalis, less often in general paresis and infrequently with meningovascular syphilis. One should note the motor tone of muscles, changes in reflexes, islands of anesthesia, loss or diminution of vibratory sense, lack of co-ordination, ataxia and defects of speech. The typical paretic speech is characterized by slurred, slow, poorly articulated words, with tremors of the lip, tongue and face, made worse by talking. The r's and l's are the consonants that give these patients most trouble. Test phrases will bring out this difficulty. Personality changes, memory defects, emotional changes, delusions of grandeur, paranoia and so forth are generally deter-

mined on the basis of history obtained from members of the family.

Skin. The entire skin surface should be examined in a good light. Scars of a healed primary lesion should be looked for on the genitals and the more frequent extragenital sites. The eruption of early secondary syphilis may be so faint as to be almost missed except with angular lighting. Early secondary syphilis usually heals without scar formation, but long-standing late secondary syphilis may scar. Late (tertiary) skin lesions may be nodular, noduloulcerative or gummatous. The nodular lesions are most common. They tend to appear on the head and face, especially the forehead at the hairline, the nose and about the mouth; the scapular and interscapular areas and the extensor surfaces of the extremities are also usual sites. These deeply seated, indurated nodules are dull red, firm and solid, and sharply circumscribed. They tend to occur in groups, forming circles or parts of circles (arcuate). The nodules are flat-topped and may be scaly, with scales slight or heaped up. The scaly areas, called squamous or psoriasiform syphilids, may mimic the scales of psoriasis, except that no bleeding points are seen when the scales are removed. Such a scaly area often turns out to be a crust, removal of which reveals a scooped-out and shallow ulcer. The nodular lesions heal without breaking down to form ulcers, whereas the noduloulcerative lesions begin as nodules but go on to ulceration. Healing takes place with scar formation, but new nodules form at the periphery of healed scars. This gives a progressive, creeping, serpiginous or arciform appearance to the involved skin. The longer it takes for late mucocutaneous lesions to appear, the fewer the lesions present.

Gummas usually develop at points of trauma; they are generally singular, but if they are multiple, only one lesion is seen in any one part of the body. This is a hard, indurated, sharply circumscribed, painless, chronic, inflammatory lesion, which is slow-growing and progressively destructive. A gumma may be so large as to involve an entire shoulder and scapula. As the color changes slowly to a dusky red, the central portion ulcerates, leaving a punched-out ulcer with a granulomatous base. This may heal in the center but continue to extend peripherally. The margin of the ulcer may be surrounded by a dark-to-purplish-red, indurated halo.

Laboratory Procedures

Some of the findings of the history and examination may immediately account for the positive reaction, whereas other findings may indicate further investigation. A biopsy may be desired for a suspicious lesion; x-ray and fluoroscopic examination of the heart, a lumbar puncture and other diagnostic procedures may be indicated. The greater problem, however, arises when the history and physical examination are negative. How is one to interpret the positive test? Does the patient have syphilis or a nonsyphilitic reaction? Obviously, a diagnosis of syphilis should not be made on the basis of one positive blood test without some supporting clinical, laboratory or historical evidence. All that can be said at this point is that one positive blood test is presumptive evidence of syphilis. In other words, the patient has syphilis unless it can be ruled out. It is therefore important to determine what diseases and conditions may produce a positive blood serologic test in the absence of syphilis.

Causes of False-Positive Tests

Fundamentally, a positive serologic test means that in the colloidal reaction between the serum and antigen, an increased amount of reagin was found in the serum, but this is encountered in other diseases and conditions besides syphilis. A positive test may occur in any of the following situations:

A technical false-positive reaction may be the result of human error; somewhere between the time when the blood was drawn to the receipt of the laboratory report, a mistake has been made by the physician, his assistant or the laboratory technician. The error may be one of mislabeling, incorrect performance of the test or wrong interpretation of its result. The blood may have undergone hemolysis or bacterial contamination or may have been oxalated, citrated or heparinized. To rule out a technical false-positive reaction, a repeat blood test, either at the same laboratory or at other laboratories, or tests on split samples should be done.

The syphiloid diseases (yaws, pinta and bejel) are not problems in New England or elsewhere in the United States. Occasionally, one sees a treated case in a migrant laborer, merchant seaman, traveler, foreign student or new United States resident. It has been our experience that in almost every case in which the syphiloid diseases accounted for a persistently positive Wassermann test, the patient mentioned or admitted that a previous attack of yaws or pinta had occurred.

These treponematoses are caused by a treponeme morphologically indistinguishable from the spirochete of syphilis. They may represent a variant of syphilis, in which the disease has been modified by environmental and other ecologic factors. In these diseases, therefore, the positive reaction is a true biologic positive and not a biologic false-positive one.

The biologic false-positive reaction is the single most important type of false-positive reaction. The diseases in which such a reaction is found most frequently and the approximate incidence of such reactions are shown in Table 1.

It is convenient from the point of view of management to divide these reactions into acute and chronic.

The acute reactions occur during or shortly after any one of a wide variety of acute infectious diseases or follow immunization. They disappear spontaneously and revert to negative, usually within three months, or at the most in six months.

The chronic biologic false-positive reaction is characterized by the absence of any acute infection or immunization within the preceding three to six months. In contrast with the acute type, it tends to persist for years, and sometimes even for a lifetime.[21]

The only infectious disease causing a chronic biologic false-positive reaction is leprosy, which is rare in Massachusetts. Single cases were reported in 1952, 1948, 1943 and 1940, all in persons entering the State for the first time. The other diseases that cause this reaction are noninfectious in origin and belong among the so-called "collagen" diseases, such as systemic lupus erythematosus, rheumatoid arthritis and periarteritis nodosa. Two other collagen diseases, dermatomyositis and scleroderma, do not cause positive serologic reactions in the absence of syphilis.

Procedures after Positive Reports

After the first report of a positive serologic test in a patient with no evidence of syphilis on history or examination, the next step is to repeat the blood test. If facilities are available, a *quantitative* test should be performed (special forms are available from the Division of Venereal Diseases, Massachusetts Department of Public Health). If the second report is negative, another specimen should be examined in a week, and if this, too, is negative, the patient may be considered to be free of syphilis and may be discharged.

If the repeat serologic report is positive, additional diagnostic steps must be taken. A clue may be obtained from the quantitative serologic report. If the test is positive in high titer, the diagnosis of syphilis is probably correct. Biologic false-positive reactions are usually characterized by low titers or by conflicting reports among a battery of tests — for example, positive flocculation and negative complement-fixation tests, or even variation in reports among a number of different flocculation tests on the same sample of serum. However, low-titer tests do not rule out the presence of syphilis.

On the receipt of a second positive report, the following steps are indicated:

Repeated complete history. This should cover the same points as the original history. The patient may now recall having had syphilis or some other venereal disease and having received treatment (for example, hip and arm injections and penicillin). He may also recollect the occurrence of syphilis in his parents. Previous blood tests may be remembered.

In addition, questions should be directed toward excluding any factor that might cause a false-positive reaction. The following lines of inquiry are indicated: Have there been febrile episodes within the past three to six months? Is there a history of an upper respiratory syndrome within the past three to six months? Was the patient immunized within the past three to six months? Did he travel, especially outside the United States?

TABLE 1. *Approximate Incidence of Biologic False-Positive Reactions in Various Nonsyphilitic Conditions.**

CONDITION	INCIDENCE OF FALSE-POSITIVE REACTION
	%
Infectious diseases:	
Bacterial:	
Chancroid	5
Leprosy	60
Pneumonia, pneumococcal	2-5
Scarlatina	5
Subacute bacterial endocarditis	5
Tuberculosis, advanced	3-5
Spirochetal:	
Leptospirosis (Weil's disease)	10
Rat-bite fever	20
Relapsing fever	30
Viral:	
Chicken pox	5
Infectious hepatitis	10
Infectious mononucleosis	20
Lymphogranuloma venereum	20
Measles	5
Mumps	? (high)
Pneumonia, "atypical"	20
Upper respiratory infections	20
Vaccinia	20
Plasmodial:	
Malaria, acute	100
Protozoal:	
Trypanosomiasis	10
Rickettsial:	
Typhus	20
Immunizations:	
Diphtheria	? (low)
Influenza or cold vaccine	(low)
Pertussis	? (low)
Smallpox	5
Scarlet fever	(low)
Typhoid fever	<5
Typhus fever	(low)
Yellow fever	(low)
Noninfectious diseases:	
Lupus erythematosus (disseminated or discoid)	20
Rheumatoid arthritis	5
Scleroderma	—
Dermatomyositis	—
Periarteritis nodosa	5
Sarcoid	5

*Adapted from Moore and Mohr.[12]

Complete physical examination. The points enumerated for the original examination should be emphasized.

Lumbar puncture. The spinal fluid should be examined at once for the cell count at the office or clinic, or within one hour at the laboratory. A globulin estimation should also be done at the office or clinic. The rest of the spinal fluid should be sent to the laboratory for total-protein and Wassermann or Hinton tests (and colloidal-gold test when necessary). If the history suggests that the patient has a condition that gives a biologic false-positive reaction, the lumbar puncture may be delayed.

A positive spinal-fluid reaction means syphilis.

False reactions occur only in easily recognized neurologic conditions, such as acute meningitis, acute lymphocytic choriomeningitis, subarachnoid hemorrhage and brain tumor.[22]

Epidemiology

Examination of the patient's contacts may prove to be of invaluable assistance in speedy diagnosis. For example, if a patient with a positive blood test for syphilis has been exposed to a person with primary or secondary syphilis, the diagnosis is obvious. Similarly, if the patient is married the spouse should be given a blood test. A positive reaction in the marital partner is more significant than a negative one. If the patient is a married woman, the children's blood as well as the husband's should be tested. A positive finding in one of the offspring will confirm the diagnosis of syphilis in the mother as well as in the child. In infants under three months, however, a positive blood test may not mean syphilis in the baby; the possibility of reagin transfer must be considered.

Evaluation of Reports

The interval between the second positive report and the patient's next visit is used to collate the various historical, clinical, laboratory and epidemiologic reports. Hospital records may show that the patient's parents had a positive serologic reaction as an incidental finding; this will strengthen the diagnosis of congenital syphilis. A Selective Service test, as well as a premarital test, may have been negative. There may have been nothing in the patient's history to indicate a recent febrile episode or acute illness or immunizations. If the clinical and epidemiologic investigations are negative, a follow-up serologic study for a three-month period is indicated. The patient should be asked to return at weekly or biweekly intervals for quantitative tests.

Obviously, the three-month study does not apply to a pregnant woman. In such a case, after a second positive reaction, treatment should be started immediately.

A significant rise in blood titer during this observation period is indicative of early syphilis. Conversely, a significant decrease in reagin titer without treatment points to an acute biologic false-positive reaction. Rises or falls in titer are considered significant if there is a variation in reaction of more than two tube dilutions from the previous report. For example, a report that originally read positive in a dilution of 1:32 and is followed by a positive report in a dilution of 1:4 indicates a significant change. The same test and laboratory must be used for both tests.

At the end of three months, if the patient continues to have a positive serologic reaction of fixed or fluctuating titer without a diagnostic pattern, he has either syphilis or a chronic biologic false-positive reaction. Most such patients have syphilis. Lupus erythematosus accounts for a majority of the cases in which a reason for the chronic biologic false-positive reaction can be established. If this diagnosis is suspected, the following tests are indicated: sedimentation rate, thymol turbidity, cephalin flocculation, total protein, with albumin-globulin ratio, and L. E. cell.

Sometimes after three months' study the physician is still unable to diagnose syphilis or eliminate it. In this event resort may be had to the *T. pallidum* immobilization test. The Division of Venereal Diseases will perform this test for Massachusetts physicians without charge on such problem cases.[23]

The interpretation of the *T. pallidum* test is as follows[24]:

A positive test means that the patient has or has had syphilis. False-positive tests are found only in yaws, pinta and bejel. In Massachusetts, however, these three diseases are imported medical curiosities.

In untreated primary syphilis, the test is positive in more than 50 per cent of the patients.

In untreated secondary syphilis, the test is positive in 95 to 98 per cent of the cases examined.

In untreated, acquired latent and late syphilis, as well as congenital syphilis, the test, for all practical purposes, is always positive.

In treated primary, secondary and early latent syphilis, the test, if positive, will revert to negative in an extremely high proportion of cases. In general, the treponema-immobilizing antibody disappears from the blood, as does reagin, but at a slower rate and not necessarily in a parallel manner. Also, if the test was originally negative before treatment, it may never become positive after treatment has been instituted.

In treated, acquired late latent and late syphilis and in treated congenital syphilis the test, even years after treatment, remains positive in a higher proportion (85 to 95 per cent) than reagin tests. If the test becomes negative, it does so over a longer period than that required for the reversal of the reagin tests.

A negative *T. pallidum* immobilization test will rule out syphilis in cases not covered by the situations enumerated above.

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MEDICAL INTELLIGENCE

LEAD POISONING AFTER INGESTION OF A FOREIGN BODY RETAINED IN THE STOMACH*

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IN children it is generally accepted that conservative measures are indicated in the management of swallowed foreign bodies once they reach the stomach. If the object is small, the period of retention in the stomach is usually short, and the patient seldom has further difficulty in passing the object. Generally these statements are valid. If the foreign body is retained in the stomach, however, each case must be managed individually, and the possibility that the object swallowed contains lead must be seriously considered.

CASE REPORT

A 23-month-old boy was admitted to Tripler Army Hospital, having been referred from elsewhere to the pediatric clinic. This patient had been under observation for 59 days after the accidental ingestion of an automobile-key-chain emblem not quite as large as a 25-cent piece. Immediately after ingestion he had been followed at a local dispensary for 2 weeks, during which he had not passed the foreign object. X-ray examination on admission to the Tripler Army Hospital Pediatric Clinic revealed that the object was still in the stomach. Because of the small size and regular shape of the object, it was decided to follow the progress of the patient by means of weekly x-ray studies of the abdomen. The films showed that the object remained in the stomach.

The parents stated that on the 38th day after ingestion the patient began vomiting almost immediately after eating and that his normally good appetite was diminished. The vomiting was occasionally described as projectile. On admission to the hospital on September 14, 1955, the parents stated that he was not retaining solids or liquids; he had lost 0.7 kg. (1½ pounds) in weight. He was admitted to the hospital because of the possibility of partial obstruction or gastritis.

The past and family histories were not pertinent to the present illness.

Physical examination showed a boy who weighed 11.3 kg. (25 pounds) and was 84 cm. (33 inches) tall. The temperature was 99.4°F. General physical examination was within normal limits, including neurologic tests. There was no evidence of dehydration, and no abnormalities were evident on examination of the abdomen. The patient's blond complexion made it difficult to evaluate pallor, but he was thought to be pale.

X-ray examinations showed a normal chest; the foreign body was still present in the stomach. Examination of the blood showed a red-cell count of 2,990,000, with a hemoglobin of 8.0 gm. per 100 ml., and a white-cell count of 13,600, with a normal differential and abundant target cells. On throat culture beta-hemolytic streptococci were found. The urine contained a trace of albumin, with 8 to 12 white blood cells per high-power field in the sediment.

The patient vomited only occasionally, but his appetite was poor. Stools were infrequent, and occasional enemas were necessary. Fluoroscopy showed the foreign body to be freely movable within the stomach. Fluoroscopy with barium meal showed almost complete retention in the stomach at 1½ hours. After 24 hours the meal was in the large bowel. Consultation with the surgical service at this time resulted in a decision to perform a gastrostomy to remove the metallic body and to explore the pylorus and terminal portion of the stomach for evidence of congenital obstruction. The anorexia, delay in emptying the stomach and continued irritability of the patient were considered due to retention of the foreign body. After 2 blood transfusions to raise the hemoglobin to 15.6 gm. per 100 ml., an operation was performed on the 68th day after ingestion, and the object was removed. There was no indication of congenital obstruction at the terminal portion of the stomach or the pylorus.

FIGURE 1. *Oxidized Emblem Removed from the Patient (Right) and New Emblem for Comparison (Left).*

The object had oxidized (Fig. 1), and a small portion of the key-chain loop broke off. It was sent to the laboratory for identification. Preliminary examination indicated the presence of lead, and a thorough analysis revealed that the emblem was made of a lead-containing solder alloy. Stained smear of the blood at this time showed profuse basophilic stippling, and x-ray study of the long bones disclosed well formed lead lines (Fig. 2). Re-evaluation of the preoperative films failed to show early deposits of lead at the ends of the growing bones. A classic lead line of the gums was not noted. Examination of the spinal fluid was negative. The parents were questioned specifically and in detail concerning the possibility of other exposure or ingestion of lead (on paint, toys, old batteries and so forth), but both were emphatic in their denial, although they checked the house completely after the diagnosis was established.

It was decided to treat the patient with calcium disodium versenate. The recommended dosage of calcium versenate is 0.5 gm. twice daily for a 13.6-kg. (30-pound) child for a 5-day course followed by a 2-day interval of rest and then a 2d 5-day course. The patient weighed 10.6 kg. (23.5 pounds) on the initial day of therapy, and it was decided to administer a dose of 0.4 gm. of calcium versenate twice daily. This dosage was given intravenously in 150 ml. of 5 per cent dextrose in water over a period of 60 minutes. No untoward effects were noted.

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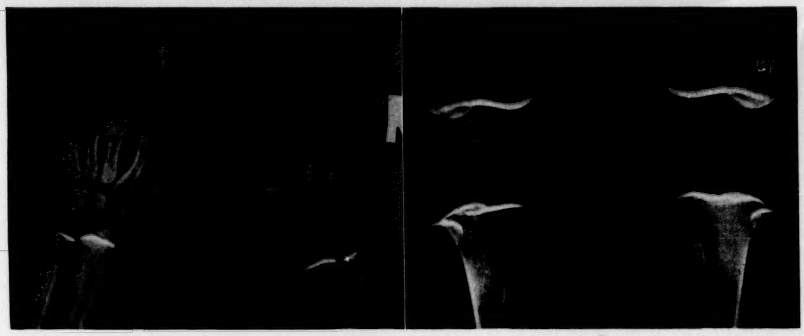
The initial serum lead determination was unsatisfactory because of technical difficulties. After the 1st course of therapy lead in the serum was 0.01 mg. per 100 ml., and after the 2d course it was reported as less than 0.01 mg. per 100 ml.

Twenty-four-hour collection of urine tested for lead was reported as showing 0.056 mg. per 24-hour specimen after the 1st course of treatment. The lead in the urine when treatment had been completed was not reported and was presumed to have been lost in the laboratory.



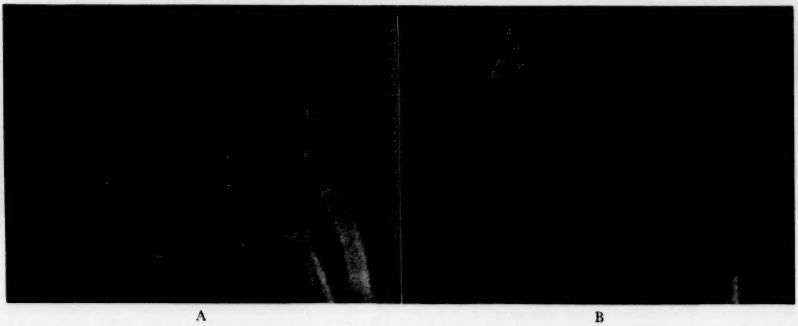
A B

FIGURE 2. *Roentgenograms of the Hands and Wrists* (A) *and the Knees* (B), *Taken Two Days after Operation, Showing the Lead Line.*

After the initial course the patient was less irritable, and his appetite improved. After the 2d course of treatment, no basophilic stippling was observed on blood smear.

The hemoglobin dropped to 10.6 gm. per 100 ml. during therapy, and a 2d transfusion of 140 and 170 ml. of whole blood was given before discharge. Prescribed medication was ferrous sulfate solution (Fer-In-Sol), 0.6 ml. twice daily. On the day of discharge x-ray examination of the long bones showed no decrease in lead line over the original diagnostic films.

Regular observation as an outpatient showed that the patient's weight had increased to approximately 13.6 kg. (30 pounds) on March 16, 1956. The hemoglobin had stabilized at 12.0 gm. per 100 ml. at this time, and repeat x-ray films of the long bones disclosed that the lead lines had receded from the epiphyseal areas, showing normal growth of the bones, and that the lead lines were becoming less distinct (Fig. 3). No further basophilic stippling was noted, and the patient, except for his usual winter respiratory infections, had been enjoying good health, according to the parents. Further blood and urine studies for lead were not possible because the patient's family had returned to the mainland.



A B

FIGURE 3. *Roentgenograms of the Hands and Wrists* (A) *and the Knees* (B), *Taken Six Months after Treatment, Showing the Present Appearance of the Lead Line.*

DISCUSSION

The arguments for conservative therapy of retained gastrointestinal foreign bodies are perhaps best presented by Gross,[1] in whose series of 766 cases surgical removal was necessary in only 43 (5.6 per cent) when the object had reached the stomach. Most of the foreign bodies were removed from the stomach and duodenum.

In the case reported above, the decision to follow conservative measures was based on several factors:

the relatively small size of the object, the lack of large projecting parts, the initial absence of symptoms and of toxicity and the motility of the foreign body in the stomach. When signs suggestive of partial obstruction and irritation were noted and barium-swallow study revealed delay in emptying of the stomach, the decision for surgical intervention was made. Preoperatively, the possibility of heavy-metal intoxication was not seriously considered.

The decision to attempt to remove the deposited lead with calcium disodium versenate was prompted because of the age of the patient and the possibility that future infection, with associated acidosis, would mobilize the lead from the bones and give further signs of lead intoxication. The use of versenate is generally accepted as the method of choice in the treatment of both the chronic and the acute forms of lead intoxication and is safer than older therapeutic measures.[2] When vomiting and marked anorexia appeared, the child was admitted to the hospital. Barium-swallow examination showed delay in emptying of the stomach, and hence it was agreed that the foreign body should be removed surgically.

Gross states that objects that are going to pass from the stomach usually do so within two or three weeks. If this operative procedure had been carried out after four weeks (two weeks before the appearance of symptoms), it is possible that the patient would have had no difficulty with lead intoxication.

Every case in which a foreign body is retained in the stomach should be managed individually. If there is a possibility of lead or other heavy-metal intoxication, a gastrostomy should be performed early, even in the absence of symptoms of irritation.

Summary and Conclusions

A case of lead intoxication in a twenty-three-month-old child after accidental ingestion of a key-chain emblem containing lead is reported. The child remained asymptomatic for approximately forty-five days and showed anorexia and vomiting with a loss of 0.7 kg. (1½ pounds) in weight and irritability of varying degree before admission on the fifty-ninth day. Surgical removal of the emblem was accomplished on the sixty-eighth day after ingestion, and analysis revealed the presence of lead. Lead intoxication was proved by x-ray study and stippling of the red cells, together with increased secretion in the urine during therapy.

Ingested foreign bodies in children should be treated conservatively. However, when heavy-metal intoxication is considered possible, early surgical removal is usually indicated.

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TOTAL BLINDNESS DUE TO DIGITALIS TOXICITY

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TEMPORARY as well as permanent blindness, although mentioned in the list of visual disorders resulting from the use of digitalis or any of its glycosides, has only rarely been encountered.[1-9]

The following case demonstrates the development of sudden total blindness during the course of cardiac glycoside therapy.

Case Report

Mrs. O.L., a 67-year-old woman, with hypertensive and arteriosclerotic heart disease and atrial fibrillation, had been in and out of hospitals for the past 3 years, with repeated episodes of congestive heart failure. During 1 admission, 2 years previously, toxic visual symptoms developed on a daily maintenance dose of 0.2 mg. of digitoxin. Upon withdrawal of the drug for a few days the chromatopsia cleared, whereupon she was placed on a reduced maintenance dose of 0.1 mg. of digitoxin, without return of the eye symptoms. She continued on this regimen until 1 year before admission, when, in an attempt to control the augmented ventricular rate without producing any toxic effect, Digoxin was given in the amount of 0.5 mg. daily. Although the desired result was thus accomplished, pleural effusion developed from time to time, requiring paracentesis. On February 3, 1955, a routine chest tap was performed for the relief of dyspnea, and 1200 ml. of clear, straw-colored fluid was withdrawn. On the following morning the patient awoke feeling quite well but in a few minutes became totally blind and was admitted to the hospital.

Physical examination showed marked weight loss, cyanosis, slight dyspnea and orthopnea. The pupils reacted well to light and accommodation, with no nystagmus. The external eye movements were normal, and the confrontation test could not be performed. Funduscopy revealed narrowed, somewhat tortuous arterioles, with increased light reflex, minimal arteriovenous compression and absence of hemorrhage, exudates or papilledema. The neck was supple, with moderate distention of the cervical veins. The thyroid gland and lymph nodes were not palpable. The chest showed slight restriction of movement on the right, with dullness to flatness in the lower right third posteriorly. Auscultation elicited numerous moist rales and rhonchi, with diminished breath sounds over both lung fields. Cardiac dullness was greatly increased, and the maximum apical impulse was felt in the 6th interspace in the midaxillary line. A Grade 3 systolic murmur was audible over the entire precordium, with atrial fibrillation, a ventricular rate of 84 and a pulse of 78. The blood pressure in both arms was 210/120, and the aortic 2d sound was greater than the pulmonic. The liver was enlarged, the edge extending about 4 fingerbreadths below the right costal margin, and the spleen extended about 2 fingerbreadths below the left costal margin. There was no paralysis or weakness of the limbs, and the legs showed a ++ edema. No masses were felt on examination of the rectum. The deep reflexes were equal, and no pathologic toe signs could be elicited. Abnormal sensory changes were absent.

Examination of the blood disclosed a red-cell count of 4,600,000, with a hemoglobin of 13.5 gm. per 100 ml., and a white-cell count of 6200, with a normal differential. Urinalysis revealed a specific gravity of 1.012 and a +++ test for albumin but no sugar. Microscopical examination

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of the sediment showed a few hyaline casts, numerous white blood cells but no red blood cells.

The nonprotein nitrogen was 45 mg., the blood urea nitrogen 26.5 mg., the blood sugar 118 mg., and the total protein 6.5 gm. per 100 ml., with an albumin of 3.5 gm. and a globulin of 3.0 gm. per 100 ml. Cephalin flocculation was + in 48 hours, and the alkaline phosphatase was 4 Bodansky units.

An x-ray film of the chest on February 6 revealed considerable cardiac enlargement in the transverse diameter, with slight effusion in the right base. An electrocardiogram taken on the next day demonstrated atrial fibrillation and left-bundle-branch block.

Three days later a consultant ophthalmologist found slight pallor of the peripheral margins of the disks, with temporal chorioretinitis and mild arterial hypertensive changes — a picture considered indicative of bilateral toxic retrobulbar neuritis. This opinion and the absence of any signs of intracranial lesion seemed to justify the suspicion of digitalis intoxication as a causative factor. The medication was therefore withdrawn, and the patient treated with bed rest, periodic oxygen administration, completely salt-free diet and mercurial diuretics. After 3 weeks there was an incipient return of vision, with differentiation of colors in flowers, correct finger count and general awareness of visitors. On the 22d day, however, pulmonary edema developed, requiring heroic measures, including phlebotomy, intramuscular injection of mercuhydrin and intravenous infusion of aminophylline and 4 ml. of Cedilanid (another digitalis glycoside). Twenty minutes later she again complained of complete blindness, and the digitalis was once more discontinued. In a week the vision slowly returned, and at the beginning of the 3d week she could recognize visitors. The cardiac status, however, continued to deteriorate, and on March 16 she died quietly during sleep. Autopsy was not performed.

Discussion

The sudden development of total blindness in an elderly patient with underlying hypertension and arteriosclerosis suggests several possible diagnoses: a cerebrovascular accident; a space-occupying intracranial lesion; retinal vascular disease in either the arteries or the veins; hysteria; and drug intoxication. The physical findings and the further progress of the disease led to the elimination of the first four hypotheses.

Although early funduscopy showed no gross abnormality, slight pallor and marginal blurring developed within a few days. This fact, coupled with the prolonged digitalis glycoside therapy, led to the suspicion of digitalis intoxication. The absence of any neurologic abnormalities was in keeping with the clinical picture usually observed in toxic amaurosis. The history of previous visual abnormalities after daily administration of 0.2 mg. of digitoxin, of their cessation upon withdrawal of the drug and of their failure to reappear on reduction of dosage strengthened this belief. Further confirmation came from the return of blindness upon intravenous injection of Cedilanid (digitalis glycoside) at a time when sight was returning after Digoxin had been withdrawn. Other observers have reported similar recurrent toxic visual symptoms on resumption of interrupted digitalis therapy. The exact mechanism responsible for the visual disturbances induced by digitalis intoxication is by no means clear. Most observers believe that the major toxic action of the drug is on the cerebral cortex.

Thus, it may be assumed that the sudden onset of total blindness in this case may be ascribed to digitalis intoxication for the following reasons: a history of previous toxic visual symptoms that cleared upon cessation of digitoxin therapy; the inability to implicate with any degree of certainty any other causative factor; the return of sight three weeks after withdrawal of Digoxin; and the development of complete blindness within twenty minutes of the intravenous administration of another cardiac glycoside (Cedilanid) at a time when normal vision was beginning to return.

60 Gramercy Park

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42251

PRESENTATION OF CASE

First admission. A twenty-eight-year-old woman entered the hospital because of epigastric pain.

Two weeks previously she noted episodes of severe, crampy epigastric pain that occasionally radiated to the back, sometimes occurred at night and was slightly relieved when she doubled herself up. These episodes continued until the time of admission. Her husband and daughter had transient episodes of fever during this time. Nine days before admission she had shaking chills, and the temperature was 101.2°F. Subsequently, she was afebrile. Two days later she was given a diet of milk and cream every two hours for two days. This caused nausea for five days, during which there were two episodes of vomiting. Six days before entry she passed 3 or 4 loose stools accompanied by crampy abdominal pain. There was no hematemesis or melena. She had noted a loss of weight of about 10 pounds during the two weeks before admission. The illness began six weeks after the termination of a normal pregnancy, which was the third in three years. She had been immunized against typhoid fever four years previously.

Physical examination showed a small, thin woman. Examination of the abdomen revealed tenderness on the left side of the epigastrium. The liver and spleen were not palpable.

The temperature was 98°F., the pulse 80, and the respirations 20. The blood pressure was 100 systolic, 70 diastolic.

Examination of the urine was negative. The hemoglobin was 15.3 gm. per 100 ml. The white-cell count, the nonprotein nitrogen and the total serum protein were normal. The paratyphoid A agglutination test was + + at a titer of 1:160, and the typhoid H agglutination was + + + at a titer of 1:20. Both paratyphoid and typhoid agglutination tests were negative one week later. Gastric analysis showed 23 units of free acid. A stool specimen gave a negative guaiac test; a culture was negative for pathogens. X-ray films of the chest and an upper gastrointestinal series were normal.

FIGURE 1. *Spot Film of the Stomach, Showing the Greatly Thickened Rugae and the Area of Ulceration (Arrows) on the Greater Curvature.*

The epigastric pain diminished to a discomfort lower in the abdomen. The patient was discharged improved on chloramphenicol on the eleventh hospital day.

Second admission (three years later). After discharge three stool cultures grew out salmonella. A barium-enema examination and an upper gastrointestinal series six months after discharge were negative. There continued to be episodes of dull pain in the epigastrium and along the left costal margin lasting from minutes to several hours for three to six weeks, with pain-free intervals lasting up to several months. She was asymptomatic during the fourth pregnancy, which terminated fourteen months before entry. Subsequently, upper abdominal pain, characterized by a gnawing, empty feeling, which was made worse by food, occurred and was associated with considerable nausea and gaseous distention as well as frequent episodes of postprandial vomiting. One week before admission she had headaches, malaise and anorexia, and the temperature rose to 100.6°F. Chloramphenicol therapy was begun the day before admission.

Physical examination showed no lymphadenopathy. Examination of the abdomen revealed tenderness in the hypogastrium on the left. The liver edge, which was tender and not definitely felt, was percussed 2

cm. below the right costal margin. The spleen was not palpable.

The temperature was 98°F., the pulse 90, and the respirations 16. The blood pressure was 110 systolic, 80 diastolic.

The urinary sediment contained rare red and white cells per high-power field. Examination of the blood revealed a hemoglobin of 12.4 gm. per 100 ml. and a white-cell count of 6000. The nonprotein nitrogen was 35 mg., the calcium 8.2 mg., the phosphorus 4.1 mg., the bilirubin 0.2 mg., the total protein 6.2 gm., the albumin 4.6 gm., and the globulin 1.6 gm. per 100 ml. The amylase was 13 Russell units, the prothrombin content 60 per cent, and the cephalin flocculation test negative. Bromsulfalein retention was less than 1 per cent. The alkaline phosphatase was 2.7 units. The Widal and brucella agglutination tests and the blood Hinton test were negative. A stool guaiac test was negative, and two stool cultures were negative for enteric pathogens. X-ray films of the chest were normal. An upper gastrointestinal series showed an ulcer crater measuring 1.5 cm. in diameter, with an elevated margin measuring 1.3 cm. about it, on the anterior aspect of the proximal portion of the gastric antrum (Fig. 1); there were enlarged rugal folds in the fundus, body and antrum; peristalsis was slow and was seen throughout the lesser curvature but only in the upper portion of the greater curvature of the stomach; the lower portion of the greater curvature showed a persistent irregularity that did not appear rigid upon palpation.

An operation was performed on the third hospital day.

Differential Diagnosis

Dr. Jacob Lerman*: As I read the protocol the thought occurred to me that the operation may have been a gastroscopy. On second thought I decided that I should not call gastroscopy an operation. Was a gastroscopy done?

Dr. Helen S. Pittman: It was done; it was the operation that was done on the third day.

Dr. Lerman: Undoubtedly, another operation was done later. I should like to ask whether or not the patient regained any weight. She had lost 10 pounds before the first admission, presumably as a result of dehydration and infection.

Dr. Pittman: No; she never did.

Dr. Lerman: Did she lose more weight after that?

Dr. Pittman: She grew thinner and thinner, but she had a baby every year.

Dr. Lerman: Some women gain weight while having babies.

Two comments may be pertinent. The rise in typhoid–paratyphoid agglutinins during an acute infection with salmonella in a woman who had had previous typhoid inoculation was probably nonspecific, for it disappeared at the end of a week, just as one would have expected. There was free acid in the gastric juice on the first admission, and I assume that it was still present during the second admission since no data to the contrary were given. I was going to ask about gastroscopy and cytology, but I suppose that this information will be given later. The x-ray findings are probably the most definite. May we see the films?

Dr. Joseph Hanelin: The examination at the first admission was reported as negative. I do not have the films of the intervening examination. There may have been some gastritis; there is excess secretion in the stomach, but the folds are not unduly thickened. A distinct change in the stomach, however, was evident in the examination at the last admission. The entire stomach at fluoroscopy apparently had lost its usual pliability, although it remained distensible. The ulcer described, I believe, is along the greater curvature of the stomach in the antrum and is surrounded by considerable irregular swelling (Fig. 1). Throughout the stomach, the folds seem severely thickened and irregular, findings that were not visible three years previously. There is no obstruction.

Dr. Lerman: To begin with, I can see no obvious relation between the salmonella infection and the subsequent lesion in the stomach. Consequently, I shall dismiss it.

The main problem is to determine whether the ulceration visualized on x-ray examination was benign or malignant. The history of intermittent pain made worse by food, associated with vomiting and often occurring at night, with periods of freedom, is suggestive of a benign ulcer and is characteristic of a peptic ulcer. Unfortunately, a malignant ulcer can cause practically the same symptoms under certain conditions so that it is difficult to make a differential diagnosis merely on the basis of the history. Dr. Hanelin, is there only elevation of the folds around the ulcer without radiation?

Dr. Hanelin: There are no radiating folds.

Dr. Lerman: The elevation is more suggestive of a malignant lesion, around which there tends to be swelling involving the greater portion of this area. It is true that under certain conditions a benign ulcer can simulate this appearance in the x-ray film because of inflammatory changes around it. This patient had a fair degree of gastritis, demonstrated by the swelling of the folds in the fundus, antrum and body of the stomach. On the whole the x-ray findings favor a malignant ulcer, but they are not entirely conclusive.

This patient had symptoms localized to the epigastrium for approximately three years. This is more consistent with a benign than a malignant ulcer. The malignant ulcer is likely to be of much shorter duration. On the other hand it can develop in a person who has had nonspecific gastric symptoms, so that one cannot be sure of this as a differential point.

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Age and sex are sometimes considered of differential importance. Most carcinomatous ulcers occur after the age of forty. They run as high as 90 per cent in some of the series. Most of them occur in males — in a ratio of 3 or 4:1. On the other hand, benign ulcers are also rare in women, but are more likely to occur in young women. Benign ulcers do occur in older women and older men. Thus, age itself is not diagnostic but in this case suggests a benign rather than a malignant lesion of the stomach.

The absence of a guaiac-positive stool favors a benign lesion. The presence of free acid does not argue for either. If there had been an achlorhydria, it would have suggested a malignant ulcer. The size of the crater is said by radiologists to be of significance. The fact that this was a large ulcer argues in favor of a malignant lesion. On the other hand, we have seen many benign ulcers of large size and many malignant ones that were small. The location in the antrum is a favorite site for a carcinomatous ulcer. Moreover, the irregularity of the gastric folds, the lack of peristalsis in the area and the swelling around the ulcer all favor a malignant lesion. A benign ulcer would not explain the fever and malaise before the second admission, nor the enlarged liver. The last consideration raises the possibility of metastases although no enlarged lymph nodes were felt and no distal metastases were described. Dr. Hanelin, are you able to judge from the x-ray films whether or not there was rigidity?

Dr. Hanelin: I gather from the description of the fluoroscopist that the sluggish peristalsis suggested loss of pliability although complete rigidity was not present.

Dr. Lerman: The absence of rigidity might argue against carcinoma, but I suppose rigidity is difficult to evaluate.

What are other possibilities? Benign tumors such as adenoma, polyp, leiomyoma, fibroma, neurofibroma and myxoma are possible. Any one of these can become ulcerated. The appearance on the x-ray film certainly does not suggest a polyp. A leiomyoma could become ulcerated on the surface, with swelling secondary to the ulceration. The duration, as well as the age and sex, is consistent with leiomyoma.

What malignant tumors besides carcinoma should be considered? Sarcoma and lymphoma are possibilities. The age, the prolonged course of two or three years, the pain and the x-ray appearance, including the lack of rigidity, are consistent with lymphoma. We have seen patients with lymphoma involving the antrum or the body of the stomach with a similar x-ray appearance, consisting of swelling, infiltration and gastritis. The absence of enlarged lymph nodes, a large spleen and anemia is against the diagnosis but does not rule it out. The presence of fever and the large liver favor it.

I shall mention some diagnoses that I considered briefly as I read the protocol. One was pancreatitis. From the symptoms alone, one might suspect that the patient had pancreatitis. This would explain only the initial symptoms, but not the later x-ray findings. Gastritis? The patient had a hypertrophic gastritis but no acute gastritis with superficial ulcerations. She undoubtedly had some condition in addition to the hypertrophic gastritis. Syphilis is a diffuse fibrotic process involving the entire stomach, usually without ulcerations. I think it can be dismissed. Tuberculosis can be a localized ulcerative process, but is almost always associated with advanced pulmonary tuberculosis. It can also be discarded.

I am inclined to choose a malignant lymphoma as my first diagnosis and a benign leiomyoma, which had become ulcerated, as my second.

Dr. Pittman: I followed this woman for many years. The symptoms between the two admissions were abdominal discomfort with soft distention, rather than pain. She felt full, bloated and uncomfortable. She lost weight slowly but progressively: she weighed 102 pounds at the time of the first admission and 96 pounds at the second admission. The brief episode of headache, malaise, anorexia and fever occurred at the height of last summer's poliomyelitis epidemic. She lived next door to a patient with one of the most severe cases of bulbar poliomyelitis that was in the hospital last summer. We admitted her to the Emergency Ward to check her for that. She received a clear report and went home, but returned two days later and said, "I have decided that I have an ulcer, even though I do feel worse when I eat." She was trained in this nursing school and remembered a patient with an ulcer who had similar symptoms.

Clinical Diagnosis

?Lymphoma of stomach.

Dr. Jacob Lerman's Diagnosis

Lymphoma of stomach, with ulceration.

Anatomical Diagnosis

Malignant lymphoma, stem-cell type, of stomach.

Pathological Discussion

Dr. J. Gordon Scannell: The operation on the third hospital day was a gastroscopy. I shall read my operative note:

> On the anterior wall of the antrum, occupying the entire surface of the gastric wall, was a nodular reddish lesion, which appeared to be rigid and obliterated the normal gastric mucosa. A rather dirty, irregular ulceration was seen in this mass. A biopsy was easily taken from the tumor.

It was my impression that we were dealing with a malignant ulceration of the anterior wall of the

stomach but that we would have to await the diagnosis from the biopsy.

DR. WINFIELD S. MORGAN: Dr. Hanelin, did the radiologist think that this was a benign or a malignant lesion?

DR. HANELIN: This was thought to be a malignant lesion and characteristic of malignant lymphoma. The large folds in the stomach, particularly well shown in the spot film, are not uncommon with lymphoma. The ulceration can appear anywhere; in the case under discussion it happened to appear on the anterior wall and the greater curvature. The fact that the stomach still had some pliability is also not uncommon with lymphoma.

DR. MORGAN: In the stomach, which was removed, there was a firm, flat lesion involving the mucosa and wall measuring 9.5 by 7.5 cm. across and close to 2 cm. thick. The microscopical sections of the stomach in the region of the tumor showed invasion and often almost complete replacement of the mucosa by tumor cells of the lymphoid series. Although there was some variation, a majority of these cells were large, with abundant cytoplasm characteristic of the stem-cell type.[1]

Dr. Schulz, do you care to comment about the x-ray therapy?

DR. MILFORD D. SCHULZ: This patient received radiation therapy to the area of resection and of the regional lymph nodes. If one is going to have lymphoma, one had better have it in the stomach, for then there will be a much better chance of survival than if it occurs elsewhere. If one has to have a malignant tumor in the stomach, it is better to have a lymphoma.

DR. MORGAN: Some 79 patients with lymphoma of the gastrointestinal tract who were operated on at this hospital from 1914 to 1953 were recently described by Allen and others.[2] I should like to mention a few points from that article. Lymphoma of the stomach was rarely diagnosed preoperatively, and the position of the lesion in the stomach did not help in the diagnosis. The average age was fifty-three years, with a range of twenty-two to eighty-one years. There was no sex difference. The duration of gastrointestinal symptoms ranged from one month to seven years, and, as Dr. Lerman pointed out, there were no specific symptoms. Over 20 per cent had obstructive symptoms; ulcer pain was frequent. There was massive bleeding in 14 per cent and blood in the stool in 60 per cent. The distribution of the lymphomatous lesions was 1 in the esophagus, 44 in the stomach, 25 in the small bowel, 8 in the cecum and 1 in the rectum. The 44 cases of lymphoma of the stomach make up only 2 per cent of the malignant tumors of the stomach seen in this hospital whereas those in the small bowel constitute 39 per cent of all the malignant tumors of the small bowel. The five-year-survival rate in the patients with lymphoma of the stomach was 58 per cent; in those with lymphoma of the small bowel, it was 33 per cent.

DR. PITTMAN: The patient received 3000 r of radiation. On discharge from the hospital she weighed 84 pounds. When I saw her seven months postoperatively she had regained weight to 91 pounds. There was no suggestion of disease. The reason that she had not regained more weight was that she had a severe dumping syndrome that interfered with eating. Only the most heroic efforts have put the 7 pounds on her.

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CASE 42252

PRESENTATION OF CASE

A thirty-eight-year-old Egyptian entered the hospital because of melena.

Two years previously he noted the sudden onset of hematemesis and melena that lasted for ten days. He was admitted to another hospital, where x-ray films demonstrated varices in the cardia of the stomach. Transfusions of blood were given, and he was discharged after fifty days. He was able to continue routine work until a year later, when mild hematemesis and severe melena necessitated further prolonged hospitalization and numerous transfusions. Another episode of melena occurred six months later. At this time the serum bilirubin was 0.3 mg., the total protein 9.3 gm., the albumin 5.3 gm., and the globulin 4 gm. per 100 ml. The thymol turbidity was 12.9 units, and the cephalin flocculation +++. The bromsulfalein retention was 12.8 per cent. Further episodes of melena requiring numerous transfusions continued to occur. Two months before entry the spleen, which was said to have been previously palpable midway between the left costal margin and the umbilicus, was felt just below the costal margin. The liver edge was palpable midway between the xiphoid and the umbilicus. The hemoglobin was 2 gm. per 100 ml. Anasarca was noted at this time. With a high-protein diet and transfusions the anasarca subsided, the hemoglobin rose to 4.5 gm. per 100 ml., and the spleen became larger, reaching its previous size. The total serum protein and the albumin-globulin ratio were said to be normal. There was no history of alcoholism or exposure to jaundiced persons or to hepatotoxins.

Physical examination showed a well nourished, pale man in no distress. There was no jaundice. The abdomen was protuberant. The liver edge was not palpable. The spleen, which was firm, smooth and

nontender, extended below the left costal margin a third of the distance to the umbilicus.

The temperature was 98.4°F., the pulse 80, and the respirations 20. The blood pressure was 110 systolic, 50 diastolic.

The urine was normal. The urinary urobilinogen was 0.7 Ehrlich units. Examination of the blood revealed a hemoglobin of 5.4 gm. per 100 ml. and a white-cell count of 1600, with 45 per cent neutrophils, 30 per cent lymphocytes, 8 per cent eosinophils, 4 per cent monocytes and 3 per cent basophils. Platelets were markedly decreased. The erythrocytes showed moderate achromia and poikilocytosis and marked anisocytosis. Considerable rouleaux formation was noted. The reticulocyte count was 1.8 per cent. The bleeding and clotting time and clot retraction were normal. The total protein was 6.9 gm., the albumin 4 gm., the globulin 2.9 gm., the bilirubin 0.7 mg., and the iron 45 microgm. per 100 ml. The sodium was 136 milliequiv., the chloride 102 milliequiv., and the potassium 3.2 milliequiv. per liter. The alkaline phosphatase was 16.9 units. The prothrombin content was 74 per cent. Cephalin flocculation was ++++ in forty-eight hours. Bromsulfalein retention was 13 per cent. The cholinesterase activity was 0.52 delta pH units per hour. A glucose tolerance test showed blood sugar values of 107 mg. fasting and 170 mg. thirty minutes, 222 mg. one hour and 96 mg. per 100 ml. two hours after ingestion of glucose. Four stool guaiac tests were negative. An upper gastrointestinal series demonstrated extensive varices of the esophagus and stomach (Fig. 1); there appeared to be some extrinsic pressure on the duodenum from the region of the liver.

FIGURE 1. *Oblique View of the Stomach, Showing Large Varices in the Fundus (Arrows).*

Numerous transfusions of blood were given, and an operation was performed on the fifteenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. H. WALTER JONES, JR.*: Hematemesis and melena recurred during a two-year period in this thirty-eight-year-old man. Hepatosplenomegaly, ascites and anemia were also prominent features of the illness. We are told that esophageal and gastric varices were found. May we see the x-ray films?

DR. JOSEPH HANELIN: The films of the gastrointestinal tract clearly show the presence of large esophageal varices. There are probably also large varices involving the gastric fundus (Fig. 1). I suspect that these are responsible for a filling defect of the fundus medially, observed in a film taken with the patient upright, with less likelihood that this particular defect results from an intrinsic neoplasm. The diaphragm is elevated, and a minute amount of fluid is noted at either base. Ascites is undoubtedly present. The spleen is enlarged.

DR. JONES: Gastric carcinoma is a possible cause of the bleeding, but I doubt if much massive hemorrhage would have gone on so long; also, it would not account for the splenomegaly or the varices. I shall assume that the varices were the source of the hemorrhages and shall not consider ulcer, gastritis or other benign and malignant tumors. The problem here is to determine why this patient had portal hypertension.

The laboratory tests indicated that the liver was involved. The thymol turbidity, cephalin flocculation and bromsulfalein tests were abnormal, and the glucose tolerance test showed a relatively high peak, with a return to normal in two hours. These findings are all consistent with parenchymal liver damage. The serum cholinesterase and the prothrombin content were low normal, and the serum bilirubin, urinary urobilinogen and serum proteins at the time of this admission were all normal. These results are not incompatible with a moderate degree of functional impairment. It is interesting that ascites occurred in the presence of a normal serum albumin, but this may happen when the portal pressure is elevated. Therefore, I believe that cirrhosis was the cause of the portal hypertension and that extrahepatic obstruction of the portal or splenic vein would not have accounted for the whole clinical picture. It is interesting that the alkaline phosphatase was also high. This may occur in cirrhosis, but it also suggests that the patient had a hepatic neoplasm, possibly a hepatoma.

Considering the etiology of the cirrhosis, we can rule out alcoholism since the patient was probably a Moslem. We are told that he had not been exposed to hepatotoxins or to other jaundiced persons. Serum hepatitis could have been transmitted by one of the transfusions, but this would have occurred after the disease was well established. We are not told any-

*Assistant in medicine, Massachusetts General Hospital.

thing about his nutritional history. We do know that he was an Egyptian. Bilharzial (schistosomal) cirrhosis is common in Egypt.

Schistosoma mansoni and *S. haematobium* are blood flukes endemic in Egypt. Human beings are infected by exposure of the skin in water infested by the cercariae. During the life cycle in the human host, the liver may be extensively involved, particularly by *S. mansoni*. The eggs and also the larvae and adult worms lodge in the smaller portal radicles, setting up a granulomatous and fibrous reaction eventuating in periportal cirrhosis. Early symptoms of invasion such as fever, urticaria, cough, abdominal pain and diarrhea were not reported in this patient. However, the infection is usually acquired in childhood while the patient is wading, and the cirrhosis may not become manifest until ten or fifteen years later. This thirty-eight-year-old man was, in fact, in the age group in which one finds the peak incidence of bilharzial cirrhosis. Hepatomegaly, sometimes with progression to a small, shrunken liver, massive splenomegaly, ascites, leukopenia, eosinophilia and anemia are prominent features of the chronic stage of schistosomiasis. Coexisting enlargement of the spleen and schistosomiasis are so frequent in Egypt that the syndrome is referred to as Egyptian splenomegaly. Esophageal varices are common in bilharzial cirrhosis. In one series of 22 cases,[1] varices were demonstrated in 12; hematemesis occurred in 10, and melena in 13. Jaundice, telangiectasia, testicular atrophy and gynecomastia, none of which are mentioned in this protocol, are less frequent in bilharzial than they are in ordinary portal cirrhosis. Liver-function tests are not distinctive.

Other flukes found in Egypt, which may cause liver damage, are *Fasciola hepatica, Dicrocoelium dendriticum* and *Coccidium cuniculi*. The protozoon disease, kala-azar, could account for splenomegaly, hepatic damage and leukopenia. However, the normal albumin-globulin ratio in this case is inconsistent with such a diagnosis.

In summary, I believe that bilharzial cirrhosis is the most probable diagnosis in this case. The persistent anemia was caused by schistosomiasis and by blood loss, as indicated by the low serum iron. The thrombocytopenia suggests that hypersplenism may have been present. This patient may also have had a hepatoma, which sometimes develops in bilharzial cirrhosis. The operative procedure may have been a shunt operation or simply a liver biopsy. Schistosomal parasites and their eggs may frequently be found in a biopsy specimen.[2]

Clinical Diagnoses

Cirrhosis of liver, bilharzial.
Portal hypertension.

Dr. H. Walter Jones, Jr.'s, Diagnoses

Bilharzial cirrhosis.
Esophageal and gastric varices.
? Hepatoma.

Anatomical Diagnoses

Schistosomiasis of liver, with portal cirrhosis (bilharzial).
Fibrocongestive splenomegaly.

Pathological Discussion

Dr. Leonard Atkins: Dr. McDermott, will you tell us your opinion preoperatively and describe the operation?

Dr. William V. McDermott: To us in this part of the world this was an extremely interesting and unique case although I am sure that to any physician

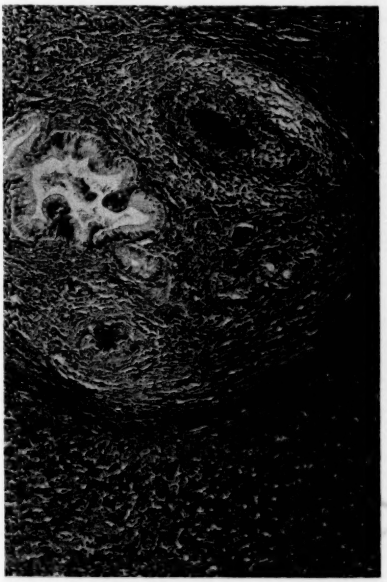

Figure 2.

with a considerable experience in the Middle East or Far East it would prove to be a much more mundane problem. Our reasoning preoperatively was much the same as that outlined so clearly by Dr. Jones. We knew the patient had esophageal varices and a severe anemia, which seemed to be a hypochromic anemia from repeated hemorrhages with the added factor of a splenic panhematocytopenia. Because of the area of the world from which this man came, the diagnosis of portal hypertension secondary to a diffuse fibrosis of the liver from a schistosome infestation seemed the

most likely possibility. One intriguing factor in the past history was the repeated observation by his physician in Egypt that with each episode of hemorrhage the splenomegaly almost disappeared only to recur when the hemorrhage ceased. We have not made this observation as definitely as this in patients with

FIGURE 3.

Laënnec's cirrhosis. Therefore, we wondered about the possibility of a splenic-vein thrombosis, possibly secondary to infestation of the portal system by the parasites, in which case a simple splenectomy should have been sufficient to control the splenic hypertension and prevent further bleeding from esophageal varices. A splenoportogram done preoperatively, however, revealed a patent splenic vein and portal system, and therefore, when the anemia had been corrected by multiple transfusions, we proceeded with a thoracoabdominal splenectomy and splenorenal shunt.

At exploration the spleen was huge; there were enormous varices in the stomach and periesophageal areas and evidence of diffuse portal hypertension throughout the abdomen. The liver appeared surprisingly normal to observation and palpation, but when a liver biopsy was taken it was apparent that a fibrotic process had occurred within the liver parenchyma.

DR. ATKINS: The biopsy specimen of the liver showed a definite increase in fibrous tissue in the portal areas that was quite marked in many places. In addition, the portal areas contained numerous schistosome ova with an associated granulomatous reaction that consisted of foreign-body giant cells, epithelioid cells, lymphocytes, fibroblasts and large numbers of eosinophils (Fig. 2 and 3). Identification of the species could not be made with certainty in our microscopical sections. Although no definite lateral spines could be seen, it seems most likely that *S. mansoni* was the cause of the disease in this case because of the known high incidence of this type of schistosomal infection in the Middle East and the predilection of this species for the portal venous system. The spleen, which weighed 1265 gm., showed congestion and dilated sinusoids.

DR. MCDERMOTT: I have recently had a letter from this patient, who returned to his home in Cairo; at present he is in excellent health, with no further gastrointestinal bleeding.

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"MEDICAL SCIENCE AND SOCIETY"

DR. Chester S. Keefer, in his scholarly Boston University Lecture, delivered on April 10, chose the broad but compelling subject of medical science and society. The progress of one and the problems of the other are very much with the world today.

The foundations of modern medical science were laid a century ago in France by Pasteur the bacteriologist and Bernard the physiologist, pioneers in introducing the scientific revolution that has so far had its most profound influence on the medical progress of the twentieth century. This revolution represented the escape from traditionalism that had its beginnings in the Renaissance, its expansion in the Age of Reason and its full flowering for modern generations in the explosive century in which man now lives. As between its art and its science medical practice is increasingly permeated by the science, and the whole profession of medicine is increasingly drawing on all the sciences for its progress.

This march of science has affected all human activities and relations, one of its most important effects having been on life expectancy; in a half century this has risen from an average of forty-six and six-tenths years to sixty-nine years for men and seventy-one years for women. As a significant effect of this shift in age the order of occurrence of the eight most common causes of death, which was tuberculosis, heart disease, pneumonia, kidney disease, accidents, cancer, cerebral hemorrhage and diarrhea and enteritis in 1911, has changed to heart disease, cancer, cerebral hemorrhage, accidents, chronic nephritis, diabetes, tuberculosis and pneumonia at mid-century.

The change in this order of frequency as well as in factors affecting health in general is largely due to the presence of an older population, more subject to chronic diseases, both physical and mental, and more prone to accidents. Deaths from the infectious diseases of youth and deaths in middle years have both decreased greatly, with a consequent increase in the degenerative diseases. In this half century of progress the population of the United States has doubled but with a tripling of those from forty-five to sixty-four years of age and a quadrupling of those sixty-five and upward.

The economic and social problems of the population are indissolubly linked with health, which in turn depends on the extension and improvement of medical research and education. The newer-older population cannot be adequately integrated into the community without the provision of an over-all cover of economic security. Health for the relatively aged, more susceptible to chronic disease and disability, costs more than for the young, comparatively untouched by these effects of superannuation. On any given day, as Dr. Keefer expressed it, 5 per cent of

the total population is disabled, but in persons over sixty-five this percentage has risen to 14.

The need of the country, in these relations, is a study of health and the factors that pertain to it, in addition to the more traditional search for knowledge about disease. There is urgent need also for the studies on aging that are being conducted by such agencies as the recently developed Age Center of New England, carried on with the eager participation of academic scientists and sociologists and industrial management itself, conscious of the part it must play in the keeping of its brother.

All this increased knowledge must depend on basic research, and this, according to Dr. Keefer, "should be the animating principle of our national policy with respect to research and it should prevail in the public sentiment. It should originate and stem from our universities." In the final analysis the objectives of medical science are the prevention of illness, the cure or amelioration of disease where prevention fails, and the rehabilitation of the disabled to a "useful, active and independent life."

BASIC RESEARCH ON TOBACCO

CANCER of the lung, like any other disease that is recognizable, can be studied at the bedside, in the laboratory or under natural conditions "in the field." Information about either cause or cure gained at any one of these levels (that of the patient himself, that of his cellular and biochemical milieux and that of his social macrocosm) supplements — it does not supplant — information gained at the other two levels. To date, most of the illuminating research on cancer of the lung has been done with sick or dead persons or in the crucible that is society itself.

The facts that have been widely publicized, and the failure of therapeutic efforts to gain a satisfactory cure and of preventive efforts to prevent, are not particularly pleasant to contemplate. Those facts and those failures are well known and are not reviewed here. They cannot be banished by advertising slogans or by reiterated asseverations that no case against tobacco has yet been proved.

How to make further progress short of abandoning tobacco is a perplexing matter, and little of enduring importance has come from vital statistics or the clinic that points to a logical solution to the smoking-cancer dilemma. "Dilemma" is used advisedly in the dictionary sense, since it involves a choice between "equally unsatisfactory alternatives." The problem is how to continue to enjoy the pleasures of smoking — fragrance, sedation, meditation and stimulation — and at the same time to sidestep its disadvantages — addiction, gastritis, bird-cage mouth, rank body-and-suit odor and cancer.

Cancer of the lung is, of course, the particular bête noire of heavy smokers — and of the cigarette manufacturers. And more embarrassing questions can be asked than can be answered about its pathogenesis: Is cancer related to the inhaling of cigarette smoke or to the mere mouthing of cigarettes? What about the fine, particulate "snuff" that can be demonstrated on a clean handkerchief after a little honking by a "heavy" smoker? Is a ceiling concentration for tar, arsenic or heavy metals contained in tobacco leaf or smoke? In this issue of the *Journal* Satterlee, reviewing the results of many years of laboratory analysis, shows that there has been a steady rise in the arsenic content of cigarette tobacco during the past twenty-five years. Explanation is doubtless to be found in the practice of spraying crops year after year with lead arsenate, which does not leach out of the soil fast enough not to affect the lead and arsenic content of fruits, vegetables or tobacco grown in subsequent seasons.

As yet the formulation of laboratory experiments bearing directly upon the pathogenesis of lung cancer has defied to an important degree ingenious efforts to harness up smoking machines to guinea-pig or rat tracheas. The conditions of human smoking simply cannot be approximated in these small animals that do not smoke. It is a constructive accomplishment, therefore, to present a fresh new laboratory approach to the problem; also in this issue of the *Journal,* Hilding has done just that. He has presented a way to measure depositions of the volatile aromatic substances of cigarette smoke in the "mucous blanket" of cattle tracheas. More important, perhaps, he has devised preparations that allow for further studies to be carried on in vivo (at least as far as ciliated epithelium is concerned) with the possibility of supplementing the information gained with that to be expected from a new laboratory approach to cancer as an anaerobic tissue, recently put forth by Warburg.*

After many years of studying the respiration of normal and abnormal cells Warburg has brought together a wealth of evidence that cancer is fundamentally an anaerobic tissue and that therein lies the key to therapy — and perhaps to prevention.

In the light of Satterlee's communication, it is interesting that Warburg selects arsenious acid as his basic example of "a strong specific respiratory poison . . . which, as every clinician knows, may produce cancer." And perhaps Hilding's method would lend itself to analysis of arsenic and arsenious acid in the mucous blanket.

*Warburg, O. On origin of cancer cells. *Science* **123**:309, 1956.

INQUISITIVE PHYSICIAN

ANY winner of a Nobel Prize acquires thereby a sort of indestructible distinction that enhances his prestige while living and clings to his memory forever. The fact that the local area has experienced a mild agglutination of these laureates in no wise de-

tracts from the permanent honor in which each is held.

Without the Nobel Prize George Richards Minot was a man distinguished in his profession; the Prize put the recognition of that fact on an international basis and added further justification for the intimate biography that has appeared under the aegis of the Harvard University Press,* six years after his death.

The story itself, entitled "The Inquisitive Physician," has lost surprisingly little in objectivity because of the circumstances under which it was written. For the author, Francis Minot Rackemann, himself a physician and investigator of distinction, was Minot's cousin, contemporary and lifelong friend and companion. This relation and the devotion that went with it have given to the book a flavor of personal and informal intimacy that has the effect of drawing the reader into the detailed existence of a cohesive, happy family group.

One of the centers of early medical culture in this country developed in that sanctified area of Boston known as the Back Bay. Not far from this hallowed, if largely man-made, plot of ground, at the foot of Beacon Hill, the Massachusetts General Hospital — known always to George Minot and others as "The Hospital," regardless of the other institutions that might come and go — had been built. In the Back Bay, on Beacon and Marlborough and their connecting streets, lived those dynasties of dedicated doctors who were privileged to serve the Hospital with a sincere if somewhat proprietary devotion. True, there was an aura of provinciality to it all, but so far as medical culture was concerned it was one of the world's great provinces.

That such a background may be fruitful is attested by the fact of the Nobel Prize, and that, of the young men who were given the opportunity to complete their training under George Minot's leadership after he became director of the Thorndike Memorial Laboratory at the Boston City Hospital, forty-six became professors of medicine in more than half the medical schools in the country.

*Rackemann, F. M. *The Inquisitive Physician*. 288 pp. Harvard University Press, 1956.

REHABILITATION RESOURCES IN METROPOLITAN BOSTON

THE recent publication, by the United Community Services of Greater Boston, of the Directory of Rehabilitation Resources in Metropolitan Boston provides a comprehensive listing of community services, primarily medical and educational, available in the area for handicapped persons. The list includes the specialized programs at rehabilitation centers, hospital services, schools, facilities for training and placement, home services and services for specific disabilities.

The growing importance of rehabilitation in the national medical picture is widely recognized, and various local facilities for this purpose have been commented on in these columns.[1-3] The Directory offers a much-needed and valuable index of the available services in Metropolitan Boston; its publication will be welcomed by all who are interested in rehabilitation as a part of medical and public-health practice.

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Bleeding at the Lungs.—*M. Aran condemns the employment of bleeding in this affection, and considers the essence of turpentine, in ten to thirty drops every hour, a valuable remedy. He speaks highly of gallic acid, in doses of two grains every hour, or every alternate hour.*

Boston M. & S. J. *June 26, 1856*

MASSACHUSETTS MEDICAL SOCIETY

GOLF TOURNAMENT

The annual golf tournament of the Society was held at the Dedham Country and Polo Club on Wednesday, May 23, with a total of 43 entries.

The winner of the first-net prize, who will have his name engraved on the Burrage Bowl, is Dr. A. J. Nicholson, with a net score of 65. Dr. F. H. Carr and Dr. James Barker tied for second place, both with a score of 68. Dr. Carr won the trophy on a tossup.

The gross first prize was won by Dr. W. R. Hill, Dr. John J. Grinold and Dr. Charles Finn tieing for second place. Dr. Grinold won the trophy on a tossup.

DEATHS

MITCHELL — Edward F. Mitchell, M.D., of Clinton, died on May 24. He was in his seventieth year.

Dr. Mitchell received his degree from Harvard Medical School in 1922. He was formerly chief-of-staff at Clinton Hospital and was a fellow of the American Medical Association and a member of the New England Heart Association.

He is survived by three brothers and a sister.

ZAWISLAK — Joseph J. Zawislak, M.D., of Lawrence, died on May 10. He was in his forty-eighth year.

Dr. Zawislak received his degree from Middlesex Medical College in 1936. He was formerly physician of the Social

Disease Clinic of the Municipal Health Department and while in New York, a member of the Academy of Medicine in Brooklyn, and was a member of the Greater Lawrence Medical Society and the Massachusetts School Physicians Association.

He is survived by his widow.

BOOK REVIEWS

A Short History of Medicine. By Edwin H. Ackerknecht, M.D. 8°, cloth, 258 pp., with 28 illustrations. New York: The Ronald Press Company, 1955. $4.50.

In this short book of a little over 200 pages, as the author states, he "deliberately limited himself to a bare outline of the history of medicine." The outline is satisfactory, and for those who need a text as brief as this, largely devoted to a series of names, dates and accomplishments, the book can be recommended. It seems doubtful, however, that it will afford sufficient factual data to satisfy either the reference librarian or the student of the history of medicine. For the former there are better textbooks easily available, and for the latter histories only slightly longer are more readable and informative. Page after page contains ten or more names with their appropriate dates, so that reading for pleasure turns out to be something of a task rather than an experience to be remembered. This is not so in all sections, for some parts of the book, where the author has presumably special interest, are much better written than others and one feels the impact of his judgment on each situation as it arises in its chronologic order.

He has the hardest time with French medicine after the Revolution. Pages are so peppered with names that they resemble the target of a double-barreled shotgun. With all inclusive dates given, a veritable "petite encyclopédie" is spread before the student, who rapidly becomes so engulfed as to lose all sense of the direction of the flow, its depth and meaning. When seventeen names appear on a page of thirty-five lines, it would take a rare student to reach a satisfactory goal over such a rock-strewn path.

Certain sections of the book need re-examination. This is particularly so of the portions devoted to American medicine. The name of the author of the first American medical publication is consistently mis-spelled. Of more importance are errors of evaluation or omissions creating false impressions. To write that "poor Boylston became the object of much abuse as a reward for his courageous innovation" of smallpox inoculation in 1721 is only a half-truth: after his decisive experiment he spent a year in England, became a member of the Royal Society and was otherwise honored by being invited to lecture before the Royal College of Physicians; returning to Boston, he won over his chief rival and became a leading practitioner as well as teacher of students.

An equally misleading conclusion is drawn about the work of Oliver Wendell Holmes on puerperal fever. A statement is made that "Holmes did not insist on his discovery; he limited himself to the teaching of anatomy and the fathering of poetry and a Supreme Court justice." Even if the facetiousness of the remark is overlooked as somewhat ill placed, the facts are not correct. Holmes did insist and vigorously. After his original paper in 1843, unfortunately published in an expiring journal, he let the pot boil until 1855, when he wrote a vigorous rejoinder, titled with one of the most provocative phrases ever used by a physician to stir up his professional brothers. Backed by the experimental work of Semmelweis in the hospital, Holmes fired both guns to such effect that puerperal fever, the dread of every pregnant woman, faded from the mortality tables within a matter of years.

HENRY R. VIETS, M.D.

Fluoroscopy in Diagnostic Roentgenology. By Otto Deutschberger, M.D. 8°, cloth, 771 pp., with 888 illustrations. Philadelphia: W. B. Saunders Company, 1955. $22.00.

This book is the first comprehensive attempt to deal with the entire subject of fluoroscopy as applied to diagnostic roentgenology and, as such, deserves the critical attention of students and practitioners of roentgenology. Actually, the work is a limited textbook of diagnostic roentgenology with special reference to fluoroscopic aspects. The format followed by the publisher is pleasing, and the illustrations both profuse and well reproduced in general. Prints are purposely positives to conform to the thesis of a fluoroscopic presentation, and for the most part are good photographically.

The introduction deals at length with various types of apparatus, and gives a very good discussion of currently available amplification devices. The principles of fluoroscopy and the hazards are well covered. A section on the localization of foreign bodies and their removal under fluoroscopic control seemed too long and detailed to this reviewer, who likewise regretted that the author did not mention the cryptoscope with more reserve.

The clinical chapters deal with the head, neck, chest, abdomen and extremities in that order. There is a good description of the procedures of myelography and of fluoroscopic checking of pneumoencephalographic studies as an adjunct to radiography. The section dealing with the neck contains a particularly good discussion on the pharynx and larynx in health and disease.

Basic principles for fluoroscopy of the chest, including the lungs and heart principally, are clearly and explicitly presented. There is some tendency to use proper names too much for phenomena and maneuvers, but this does not detract from the clarity of presentation. The diagrams in this section are excellent and most helpful. Since the author is trying to discuss a subjective study, fluoroscopy, he purposely tends to emphasize fluoroscopy at times when he might normally prefer radiography. This is particularly true of the lungs.

The section on the abdomen deals principally with the gastrointestinal tract, which is covered most ably and thoroughly. The steps of gastrointestinal fluoroscopy enumerated are admirable and clearly set forth, and constitute a description of a complete examination. Of secondary importance is the mention given to fluoroscopy of the urinary passages and the female genital tract, but as the author states, it is possible that increasing use of image amplification devices will encourage this rather neglected technic.

The final chapter on extremities deals briefly with the fluoroscopic reduction of fractures. This reviewer cannot agree that such procedures are necessary, except under most unusual circumstances.

Each chapter is supplied with a very extensive bibliography, covering particularly well the basic historic papers on each subject.

This book is recommended strongly to all roentgenologists, both in training and in practice, and to clinicians who may perform fluoroscopy, particularly the internist, cardiologist and gastroenterologist.

STANLEY M. WYMAN, M.D.

High Blood Pressure. By George White Pickering, M.A., M.B. (Cantab.), M.D. (Ghent), F.R.C.P. 8°, cloth, 547 pp., with 106 illustrations, 5 in color, and 23 tables. New York: Grune and Stratton, 1955. $9.50.

This book on high blood pressure will be of value to medical scientists whether in school, in laboratory or in practice. It details the anatomicophysiologic basic and clinical data, prognoses and treatment up to this year as Fishberg's work in 1954 and Schroeder's in 1953 did. Dr. Pickering speaks in the language of science — namely, mathematics — but ends each chapter with a succinct summary for the harrassed and hurried, and has ten pages of practical points on examination and management. The book is a clear statement of matured opinions by one of the world's leading investigators of hypertension and, with a note from one other source, is in a way — like any author's textbook — an autobiography of his scientific life to date.

Dr. Pickering recognizes a difference between high and low blood pressures, but only of degree, not of kind — quantitative, not qualitative, whether benign or malignant — since the beauty of homeostasis, like the sun, shines on high and low alike. He points out that of persons with hypertension those with the higher blood pressures die sooner, and that increasing age, inheritance and more important but less

completely assessed environmental factors, such as overweight and influences operating through the mind, as well as certain specific diseases, may separately or in combination elevate the blood pressure, which, when raised long enough by a specific cause, may remain high when the specific cause no longer operates. The indications for lowering the blood pressure he considers to be papilledema, fits, loss of cardiac reserve, unexplained hematuria and albuminuria if the pressure is grossly elevated — a diastolic pressure of 140 at and over forty and 130 under forty years of age. He suspects, though he is not sure, that more may be gained than lost if the blood pressures of hypertensive patients with the angina pectoris, myocardial infarction and cerebral accidents are lowered.

In this suspicion I believe that he is incorrect; I agree with his suspicion that diet and anticoagulants are more important and that prevention of strokes, indeed the whole mystery of vascular sclerosis, remains. Like him, I prefer treatment with less nuisance value than attaches to most of the hypotensive drugs currently in use, and recommend the rice diet to him, though he reports that in Great Britain it "disrupts social relations" and besides is "insipid, unappetizing and monotonous." Perhaps observer error, of which Dr. Pickering is so careful, operates here since he implies that he himself is free from the Victorian sense of sin that he thinks afflicted some of his teachers and may have led them to proscribe the pleasures of table, bottle and nicotine.

Perhaps this is only an echo of the young physiologist in Lewis's laboratory twenty-three years ago who recently confessed elsewhere that the problem of hypertension at that time appeared a relatively simple one to solve. It has been a long step from the laboratory experiments of those days to the present when "it was as though the veil had been lifted" with the illuminating clinical realization "that the problem of the cause of essential hypertension is the problem of the cause of the variations in pressure in the population at large." I submit that the environmental factor in hypertension that Dr. Pickering seeks is as natural as the variations in blood pressure and that it differs in degree, not in kind, for all men, participates in the etiology of the windy melancholy, character cramps, personality growing pains and general aging, is productive of more blood-pressure-raising privations than original nature herself and, in short, is the second nature of civilized man's own contriving. With the new responsibilities and opportunities as Regius Professor of Medicine in Oxford, in which we wish him well, perhaps Dr. Pickering will avail himself of the technics of new colleagues in the social sciences in elucidating the role of culturally induced character traits in hypertension and other conditions of civilized man, even though the only cure for the birth and death of the hypertensive patient or anyone else may be to enjoy the interval circumspectly.

ROBERT S. PALMER, M.D.

Classics of Biology. By August Pi Suñer. With authorized English translation by Charles M. Stern. 8°, cloth, 337 pp. New York: Philosophical Library, 1955. $7.50.

Dr. Pi Suñer, who is well known as a physiologist from the University of Barcelona and who has written many outstanding papers in his field, sets down his ideas on the significance of the classic contributions to biology in general by his predecessors. He has chosen three or four distinct contributions on such subjects as the cell theory, metabolism, heredity, reproduction, consciousness and the will. Extracts from these papers, consulted in the original language, were first translated into Spanish and now into English, except when the first paper appeared in the English language itself. The translations are excellent and often give a fresh reading to a paper in a language such as Russian not easily read by most physiologists and historians. Of more importance, however, are the introductory notes to each chapter by Dr. Pi Suñer himself. Here he has not only summarized the work that was done by his predecessor but also placed it in the history of the development of the idea. Some will disagree with his choice of authors, and others will note that he has not included some that should rightfully belong in a book of this type. Nevertheless, what he has provided is important and useful, and the subject in general is well covered. This book is a useful reference book, but also may be read with pleasure by anyone interested in the history and development of ideas and, indeed, will afford a conception of how much has been accomplished in the past and what paths are now open for future endeavors.

HENRY R. VIETS, M.D.

The Body Fluids: Basic physiology and practical therapeutics. By J. Russell Elkinton, M.D.; and T. S. Danowski, M.D. 8°, cloth, 626 pp., with illustrations and tables. Baltimore: The Williams and Wilkins Company, 1955. $10.00.

This work is a testimony not only to the authors' many contributions to the literature over a period of years, but also to their comprehensive knowledge of many aspects of the literature on body fluids. In general the book is well written (although it suffers somewhat from chapter-by-chapter repetition) and should become a valuable reference book. From the point of view of a general textbook for the physician who is not primarily interested in the physiology of body fluids, it has several shortcomings. Chief among these is the failure to include in sufficient detail in the chapter-by-chapter development the role of and function of the kidneys in the economy of body fluids.

Secondly, data pertaining to the composition, metabolism and acute and chronic changes in the intracellular fluid have been emphasized throughout the volume. Although the authors point out the potential errors involved in calculating the volume and composition of body-water compartments (based on a series of formulas), they fail to point out to the reader the controversial nature of conclusions based on these calculations.

Among positive features of the book one must include a literary style that neatly ties together many abstract facts into comprehensive concepts. Finally, the chapter, "Paleochemistry, Evolutions and Comparative Physiology of the Body Fluids," is outstanding. Of particular importance to the student of clinical research is an excellent appendix illustrating balance technics and their interpretation. This should be read by every investigator beginning in this field. The general emphasis, however, is for the investigator rather than for the clinician. The figures illustrating balance studies are complex and require careful study. As an example it is to be noted that two full chapters are devoted to "disease states resulting in an excess of water or electrolytes" and the therapy of excesses of water or of the chief electrolytes, whereas only one page is devoted "to the treatment of congestive heart failure." Thus, the emphasis is on basic abnormalities and their correction, rather than on the approach to the clinical syndrome. Although the bibliography is large, it is not totally comprehensive in that the majority of contributions represent largely the work of one school of thought. This certainly does not detract from the work as a reference source, but does make it less valuable for the uninitiated reader.

NEAL S. BRICKER, M.D.
JOHN P. MERRILL, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Anesthesia: Thief of pain. By Sylvan M. Shane, attending anesthesiologist, Lutheran Hospital of Maryland, chief of anesthesiology, Doctors Hospital of Baltimore, and consultant anesthesiologist, Spring Grove Hospital of Maryland. With an introduction by Henry E. Sigerist, Department of the History of Medicine, Yale University School of Medicine. 8°, cloth, 87 pp. New York: Vantage Press, 1956. $2.50.

Obstetric Practice. By Harold Speert, M.D., associate in obstetrics and gynecology, Columbia University College of Physicians and Surgeons, and assistant attending obstetrician and gynecologist, Presbyterian Hospital, New York City; and Alan F. Guttmacher, M.D., director, Department of Obstetrics and Gynecology, Mount Sinai Hospital, New York City, and clinical professor of obstetrics and gynecology, Columbia University College of Physicians and Surgeons. 8°, cloth, 478 pp. New York: Landsberger Medical Books, Incorporated, 1956. $7.00. (Distributed solely by the Blakiston Division of the McGraw-Hill Book Company.) (*Handbooks for the General Practitioner.*)

Laboratory Tests in Common Use. By Solomon Garb, M.D., assistant professor of clinical pharmacology, Cornell University Medical College. 12°, cloth, 160 pp., with 15 tables. New York: Springer Publishing Company, Incorporated, 1956. $2.00.

The Rochester Regional Hospital Council. By Leonard S. Rosenfeld, M.D., M.P.H.; and Henry B. Makover, M.D. 8°, cloth, 204 pp., with 22 tables. Cambridge, Massachusetts: Harvard University Press, 1956. $3.50. (Published for the Commonwealth Fund.)

Modern Treatment Yearbook 1956: A yearbook of diagnosis and treatment for the general practitioner. Edited by Sir Cecil Wakeley, Bt., K.B.E., C.B., LL.D., M.Ch., D.Sc., F.R.C.S., F.R.S.E., F.R.S.A., F.A.C.S., F.R.A.C.S., senior surgeon, King's College Hospital, director of surgical studies and lecturer in surgery, King's College Hospital Medical School, senior surgeon, Belgrave Hospital for Children and Royal Masonic Hospital, consulting surgeon to the Royal Navy and examiner in surgery to the University of Cambridge. 8°, cloth, 367 pp., with 47 illustrations and 6 tables. London: The Medical Press, 1956. $6.00. (Distributed in the United States by the Williams and Wilkins Company, Baltimore.)

Collagen Diseases: Including systemic lupus erythematosus, polyarteritis, dermatomyositis, systemic scleroderma, and thrombotic thrombocytopenic purpura. By John H. Talbott, M.D., professor of medicine, University of Buffalo School of Medicine, and physician-in-chief, Buffalo General Hospital; and R. Moleres Ferrandis, M.D., training fellow in arthritis of the Western New York Chapter of the Arthritis and Rheumatism Foundation. 8°, cloth, 232 pp., with 30 illustrations and 16 colored plates. New York: Grune and Stratton, 1956. $6.50.

Vorträge aus dem Gebeit der klinischen Chemie und Cardiologie. By Prof. Dr. L. Heilmeyer, director, Medizinischen Universitätsklinik, Freiburg i. Br. 8°, cloth, 96 pp., with 70 illustrations, 10 tables and 1 colored chart. Stuttgart: George Thieme, 1956. DM 10.80.- $2.60. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Dynamics of Psychotherapy: The Psychology of Personality Change: Principles. By Percival M. Symonds, Ph.D., professor of education, Teachers College, Columbia University. 8°, cloth, 211 pp. New York: Grune and Stratton, 1956. $5.50.

Basic Otolaryngology. By Francis L. Lederer, M.D., professor of otolaryngology and head, Department of Otolaryngology, University of Illinois College of Medicine, chief, Otolaryngological Service, Research and Educational Hospital, Chicago, and director of otolaryngology and chief, Ear, Nose, and Throat Service, Illinois Eye and Ear Infirmary, Chicago; and Abraham R. Hollender, M.Sc., M.D., clinical professor of otolaryngology, University of Miami School of Medicine, and consulting otolaryngologist, St. Francis Hospital, Miami Beach, Variety Children's Hospital, Miami, and Mount Sinai Hospital, Miami Beach. Fourth edition. 8°, cloth, 453 pp., with 208 illustrations and 11 colored plates. Philadelphia: F. A. Davis Company, 1956. $6.75.

Health and Travel: Proceedings of the First International Symposium on Health and Travel held in New York City, June 23, 1955. Félix Martí-Ibáñez, chairman. 8°, paper, 70 pp., with illustrations and tables. New York: MD Publications, Incorporated, 1956.

Pulmonary Carcinoma: Pathogenesis, diagnosis, and treatment. Edited by Edgar Mayer, M.D.; and Herbert C. Maier, M.D. 8°, cloth, 540 pp., with 182 illustrations and 4 colored plates. New York: New York University Press, 1956. $15.00. (Distributed by the J. B. Lippincott Company, Philadelphia and New York City.)

Studies from The Rockefeller Institute for Medical Research. Reprints. Vol. 151. 8°, paper, 559 pp., with illustrations, tables and plates. New York: The Rockefeller Institute for Medical Research, 1956.

The Legacy of Sigmund Freud. By Jacob A. Arlow, M.D. 12°, cloth, 96 pp., with a frontispiece. New York: International Universities Press, Incorporated, 1956. $2.00.

The Diagnosis and Treatment of Postural Defects. By Winthrop Morgan Phelps, M.D., medical director, Children's Rehabilitation Institute for Cerebral Palsy, Baltimore, and consultant in cerebral palsy for the states of New York, New Jersey, Delaware and Pennsylvania and others; Robert J. H. Kiphuth, M.P.E., professor of physical education, Yale University; and Charles Weer Goff, M.D., associate clinical professor of orthopedic surgery and lecturer in anatomy, Yale University School of Medicine, attending orthopedic surgeon, Newington Home and Hospital for Crippled Children, and visiting professor of physical anthropology, Hartford Seminary Foundation. Second edition. 8°, cloth, 190 pp., with 87 illustrations and 1 table. Springfield, Illinois: Charles C Thomas, 1956. $6.50.

In the Doctor's Office: The art of the medical assistant. By Esther Jane Parsons. Second edition. 12°, cloth, 326 pp., with 11 illustrations by Jean McConnell. Philadelphia: J. B. Lippincott Company, 1956. $3.95.

The Sexual Responsibility of Woman. By Maxine Davis. With an introduction by Lester S. Blumenthal, M.D. 8°, cloth, 299 pp. New York: The Dial Press, 1956. $4.00.

Psychoanalysis and Psychotherapy: Developments in theory, technique, and training. By Franz Alexander, M.D., director, Chicago Institute for Psychoanalysis, and clinical professor of psychiatry, University of Illinois College of Medicine. 8°, cloth, 299 pp. New York: W. W. Norton and Company, Incorporated, 1956. $4.75.

Hunterdon Medical Center: The story of one approach to rural medical care. By Ray E. Trussell, M.D., M.P.H., executive officer, Columbia University School of Public

Health and Administrative Medicine. 8°, cloth, 236 pp., with 9 illustrations and charts. Cambridge, Massachusetts: Harvard University Press, 1956. $3.75. (Published for the Commonwealth Fund by the Harvard University Press.)

A Handbook of Medical Hypnosis: An introduction for practitioners and students. By Gordon Ambrose, L.M.S.S.A., hon. consultant psychiatrist, Park House Approved School, Guildford, sometime psychiatric registrar, Banstead Hospital, Sutton, Surrey, and member of the Society for Clinical and Experimental Hypnosis, New York; and George Newbold, M.B., B.S., M.R.C.S., M.M.S.A., D.R.C.O.G., D.C.H., member of the Middle Temple, member, Medico-Legal Society, and member of the Society for Clinical and Experimental Hypnosis, New York. With forewords by William Moodie, M.D., F.R.C.P., D.P.M., consultant physician, University College Hospital, London; and William S. Kroger, M.D., associate professor of gynecology, Chicago Medical School. 8°, cloth, 255 pp. London: Baillière, Tindall and Cox, 1956. $5.00. (Distributed in the United States by the Williams and Wilkins Company, Baltimore.)

Gynecologic Cancer. By James A. Corscaden, Ph.B., M.D., attending gynecologist, Sloane Hospital for Women, New York. Second edition. 8°, cloth, 546 pp., with 116 illustrations and 43 tables. Baltimore: The Williams and Wilkins Company, 1956. $10.00.

Ergebnisse der gesamten Tuberkuloseforschung. Vol. 13. Edited by St. Engel, London, L. Heilmeyer, Freiburg/Br., J. Hein, Tönsheide, and E. Uehlinger, Zürich. 4°, cloth, 660 pp., with 160 illustrations. Stuttgart: Georg Thieme, 1956. DM.- 96.- $22.85. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Ergebnisse der medizinischen Grundlagenforschung. Edited by Prof. Dr. K. Fr. Bauer, Erlangen. 4°, cloth, 856 pp., with 217 illustrations and tables. Stuttgart: Georg Thieme, 1956. DM 129.- $30.70. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Grundriss und Atlas der gynäkologischen Cytodiagnostik. By Dr. H. Smolka, assistant, Universitäts-Frauenklinik, Kiel; and Dr. H. J. Soost. With a foreword by Prof. Dr. E. Philipp, Dr. Med., professor-in-ordinary and director, Universitäts-Frauenklinik, Kiel. 4°, cloth, 166 pp., with 186 illustrations and 6 figures. Stuttgart: Georg Thieme, 1956. DM 120.- $28.55. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Atlas und kurzgefasstes Lehrbuch der Phonokardiographie und verwandter Untersuchungsmethoden. By Priv.-Doz. Dr. med. K. Holldack, Medizinische Universitäts-Poliklinik, Heidelberg; and Dr. med. D. Wolf, Universitäts-Kinderklinik, Heidelberg. With a foreword by Prof. Dr. K. H. Bauer, Heidelberg, and a technical introduction by F. Schwarzer, Munich. 4°, cloth, 171 pp., with 179 illustrations and 7 tables. Stuttgart: Georg Thieme, 1956. DM 49.50. $11.80. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Die Röntgenbildanalyse: Eine röntgendiagnostische Anleitung für Studierende und Ärzte. By Prof. Dr. Erich Saupe. Third edition, revised by Prof. Dr. W. Teschendorf, Cologne. 4°, cloth, 283 pp., with 328 illustrations. Stuttgart: Georg Thieme, 1956. DM. 49.50. $11.80. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

NONCLINICAL NOTES

RHODE ISLAND MEDICAL JOURNAL

Dr. John E. Donley, past president of the Rhode Island Medical Society and the medical director of the Rhode Island Curative Center, has been named as the new editor-in-chief of the *Rhode Island Medical Journal,* succeeding the late Dr. Peter Pineo Chase. John E. Farrell, executive secretary of the Society, continues as managing editor.

Dr. Donley, one of the Society's most distinguished members, was the recipient of the City of Providence Charles V. Chapin medal award a year ago, and in 1953 he received a citation from President Eisenhower's Committee on National Employ the Physically Handicapped for his "outstanding services to the disabled" in Rhode Island.

A past president of the Providence Medical Association and the Rhode Island Society of Psychiatry and Neurology, as well as the state medical society, Dr. Donley is a member of the staffs of the major hospitals in the State. He has been chairman of the Publications Committee of the Society for more than ten years. He has been the recipient of honorary doctor of laws degrees from Providence College and Seton Hall University for his outstanding work in medicine.

NOTICES

ANNOUNCEMENT

Dr. Sidney C. Dalrymple announces the reopening of his summer office in Georgetown, Maine.

SOCIETY MEETINGS AND CONFERENCES

June 22. Medical Library Association. Page 1051, issue of May 31.
June 22 and 23. Society of Nuclear Medicine. Page 1092, issue of December 15.
June 22–24. American Academy of Dental Medicine. Page 994, issue of December 1.
July 1–6. International College of Surgeons. Page 1148, issue of June 14.
July 9. Fifth Annual Symposium for General Practitioners. Page 1010, issue of May 24.
August 19–23. American College of Chest Physicians. Page 840, issue of November 10.
September 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.
September 10–14. American Dietetic Association. Page 1180, issue of December 29.
October 30 and 31 and November 1. New England Postgraduate Assembly, Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, JUNE 28

THURSDAY, JUNE 28

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.

(Concluded on page xxxii)